DISSERTATION ON

"THE PREVALENCE AND CLINICAL IMPACT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS IN RESISTANT ASTHMATICS ON TREATMENT IN THE RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL "

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CERTIFICATE

This is to certify that the dissertation entitled "THE PREVALENCE AND CLINICAL IMPACT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS IN RESISTANT ASTHMATICS ON TREATMENT IN THE RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL "is a bonafide work done by **DR H GOKULAKRISHNAN** , post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai-3 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic period from may 2010 to april 2013.

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DECLARATION

I solemnly declare that the dissertation entitled "THE PREVALENCE AND CLINICAL IMPACT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS IN RESISTANT ASTHMATICS ON TREATMENT IN THE RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL "is done by me at Madras Medical College, Chennai-3 during May2010 – April 2013 under the guidance and supervision of Prof.R.Penchalaiah M.D, to be submitted to The Tamilnadu Dr M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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CONTENTS

INTRODUCTION

Hinton and Peppy et.al described Allergic bronchopulmonary aspergillosis as a disease characterised by hypersensitivity to Aspergillus antigen occurring in immunocompetent persons ,associated with spectrum of disease like steroid dependent asthma and cystic fibrosis.

Patterson and Greenberg did pioneering studies in the prevalence and pathogenesis of allergic bronchopulmonary aspergillosis and proposed diagnostic criteria.

It often masquerades as bronchial asthma with frequent exacerbations and difficulty in tapering steroids. It is one of the progressive disease not only causing serological change but also spectrum of changes in the parenchyma and airways characterized by central bronchiectasis and fleeting opacities.

By identifying and classifying this disease, we can prevent worsening of asthma and also can retard the relentless progression of allergic bronchopulmonary aspergillosis.

On chest radiograph, fleeting opacities may resemble pulmonary tuberculosis resulting in inappropriate treatment as drug resistant

tuberculosis. To diagnose ABPA as a cause of the radiological shadow, high index of suspicion is warranted.

Genetic susceptibility has also been documented in patients with HLA- DR2 and HLA-DR5 showing increased propensity to Allergic Bronchopulmonary Aspergillosis patients with HLA DRQ2 have reduced susceptibility.

It is imperative to consider ABPA in patients who are resistant and refractory to standard protocol based treatment for bronchial asthma. The importance lies on the fact that, on correct identification and with appropriate treatment, patients can be relieved of their ordeal .Thereby the patient's quality of life can be improved with increased disease free interval and reduced workplace absenteeism.

In this study we attempt to diagnose and stage ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS its prevalence and its association with bronchial asthma, Asthmatics who were refractory to protocol based treatment and clinical impact of ABPA over Asthma patients.

AIMS AND OBJECTIVES

1.To findout the prevalence of allergic broncho pulmonary aspergillosis in patients with resistant asthma.

2.To identify the clinical and laboratory pointers of ABPA.

3.To identify the effect of ABPA and and its treatment on the course of resistant asthma.

OBJECTIVES

Primary Objective is to study about ,

"THE PREVALENCE AND CLINICAL IMPACT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS IN RESISTANT ASTHMATICS ON TREATMENT IN THE RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL "

Secondary Objectives are

a) To assess the disease severity and treatment modification for control in asthmatics due to the coexistence of allergic broncho pulmonary aspergillosis
b) To assess the prognosis periodically and at the end of 6 months after the modification of treatment.

Study design

The study is a Prospective , uncontrolled and non-blinded study done in both out-patients and in-patients.

Period of study: 6 months

Ethical Clearance:

Approved by the ethical committee of Madras Medical college

Consent

Written informed consent from all patients or their relatives

REVIEW OF LITERATURE

INTRODUCTION

Allergic broncho pulmonary aspergillosis is a disease of individuals with atopic asthma , which is steroid responsive. It is characterised by mild wheeze , golden brown sputum with mucus plug into proximal airways causing disease spectrum varying from mild exacerbation of the disease to severe respiratory failure and pathological changes like terminal musculo cartilaginous destruction , central Bronchiectesis and upper lobe parenchymal disease .Though this disease is considered as a rare entity , most of the time what we see is the tip of the iceberg where most of the disease is submerged among the difficult to control asthma and and a small number of group of people with cystic fibrosis

HISTORY;

It was first reported in Great Britain in late 18th century and reexplored by HINTON in 19 50s and his co workers who described the universal nature of the causative organism It is still designated as idiopathic by HINTON et al and revised by PEPYs and coworkers as allergic inflammatory pulmonary disease to aspergillus species and mycelia

colonised in the bronchi. The disease spectrum occurring in difficult to treat asthma patients and about 7 to 15 percent of steroid responsive asthma affecting age group of early20's to 40 years of people.

DEFINTION

Allergic bronchopulmonary aspergillosis is a hypersensitive disorder caused by a fungus aspergillus species commonly fumigatus ,flavus,niger etc., occurring in asthmatic and ,atopy prone individuals or those with cystic fibrosis triggerred by an exposure to aspergillus spores colonising the proximal airways and the their mucus plugs in the persons who are immunocompetent with little or no tissue invasion . It is a Th2 mediated reaction with eosinophilic response and inflammation

It is a disease manifesting commonly in difficult to treat asthma patients and cystic fibrosis where there is impaired mucosal clearance of the secretion with sprouting of spores into mycelia which colonise the bronchi and mucus plugs.causing

1. Asymptomtic course

2. Cough with wheeze ,golden brownish productive sputum that contains the organism ,low grade fever, myalgia and other constitutional symptoms.

3. During the prolonged unrecognised course patients can be affected by collapse, consolidation without any volume loss or chronic fibrotic pulmonary parenchymal lesion like scarring

4. Affected individuals suffers recurrent and frequent exacerbations, cystic, cylindrical, central or proximal bronchiectasis.

Criteria for the diagnosis of ABPA

1. Known Asthmatic
2. Skin prick test positive to *Aspergillus sp*
3. Raised serum IgE concentration (>1000 ng/ml)
4. Elevated serum specific IgE levels
5. Serum Precipitin level
6. Absolute Eosinophil count

7. Chest X ray evidence
8. Proximal Bronchiectasis

MORTALIY AND MORBIDTY:

Though the mortality is less likely and occurs only in extreme illness.

Causes leading on to mortality were enlisted as

- Resistant secondary bacterial infections with organisms like pseudomonas in the preexisting dilated airways
- Progressive desaturation and respiratory failure
- Corpulmonale

Significant morbidity can be noted due the following reasons

- It is due to poor asthma control.
- Difficulty in tapering off corticosteroids and other drugs
- Airways destruction like bronchiectasis
- Parenchymal scarring

FREQUENCY

How common the ABPA is still a subject of research with various statistical datas from various corners of the world. Yet unique and

concrete criterion are lagging to suspect and to coin the patient as ABPA leaving the disease submerged in refractory asthma

Positive intradermal test for aspergillosis is seen in 24%of asthmatics and nearly half of the patients with cystic fibrosis ,8 to 16 % of the steroid dependent asthma who have associated central bronchiectasis.

One another statistical study conducted in India by using Rosenberg criteria gives 52% positivity in 356 asthmatic individuals

GENETIC PREDISPOSTION:

Human Leukocyte antigen major histocompatibility complex mainly DR 4 DR5, DR 2 are associated with increased incidence of the disease where as DRQ2 has a protective role.

DEMOGRAPHY

Occurence of allergic bronchopulmonary aspergillosis has been documented in 2^{nd} , 3^{rd} and 4^{th} decades, though it may occur in any

extremes of life and cases have been reported in these age groups .ABPA is under reported despite its large occurrence .

Puzzling and confusing factors are the principal manifestation and hence there is remarkable misperception with other clinical conditions and infectious diseases

Migratory shadows disappear once the patients coughs out and hence this roentgenographic shadows are often misleading and treated as some other diseases especially as resistant tuberculosis allowing the disease to progress with its image mimicry.

The disease if not doubted is hard to diagnose and diagnosis at an early stage is mandatory because ABPA may leave significant structural damage as the immunity wanes off over the course of time.

Outpatients attending the emergency outpatient departments with a wheeze and cough are given symptomatic treatment and disposed with drugs and injections In these patients ,the follow up is lost, owing to the relief offered temporarily by the medications given to them . Imaging and routine investigations were not done in those patients. Suspiscion was not posed due to decreased awareness and also the cost benefit ratio of those patients attending at odd hours of emergency ops.

GENDER

Incidence is more or less equal in both the genders .Atopy plays a major role in females. Occupational exposure plays a major role in females but there is no genetic or hormonal evidence for sex predilection. Prevalence in various ethnic group is not documented.

OCCUPATION

The allergen is ubiquitous but certain occupation are at increased risk like farmers, wooden workers, sewage workers etc., Special emphasis of ABPA over asthma in occupational context in atopy in individuals is not like that in exercise induced asthma.

SOCIOECONOMIC STATUS

Low socioeconomic income group are more at risk

SOURCE

Chopped grasses , sewage , wet basement of buildings are the household sources. It is universally present in paddy fields and decomposing vegetables.[6]

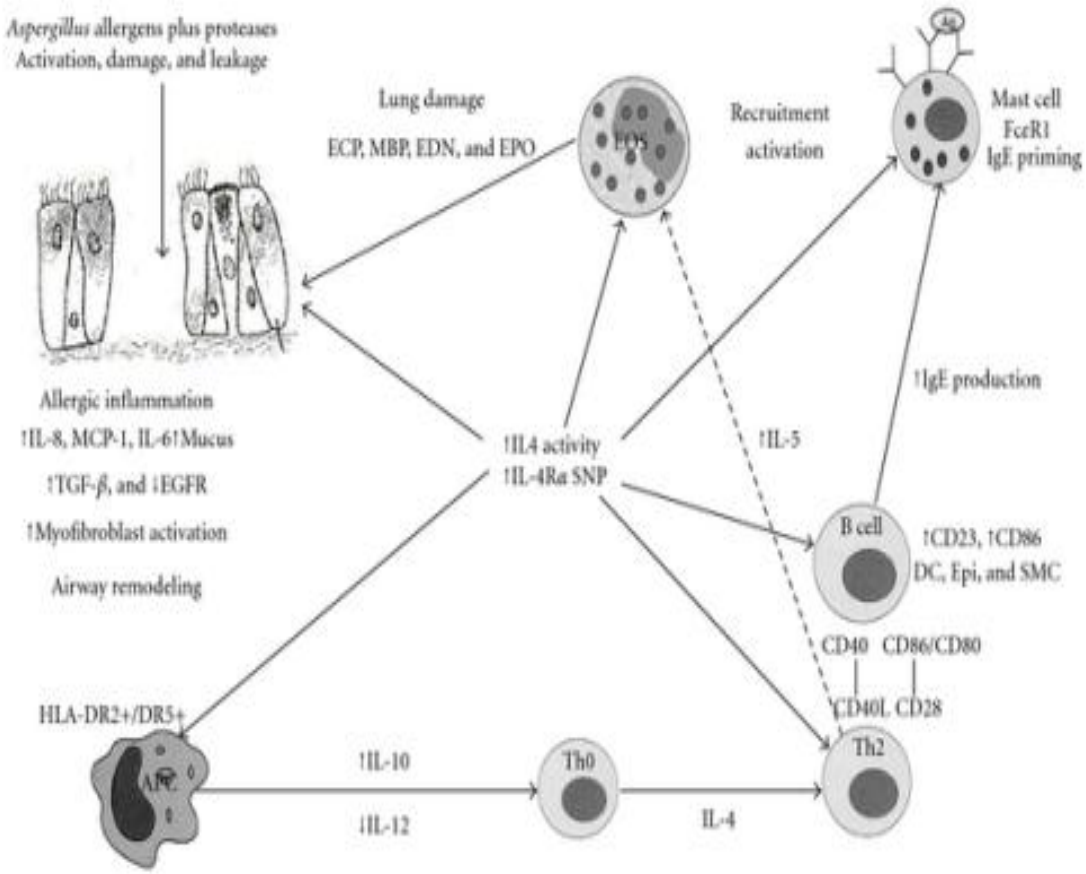
MASON et al. says saprophytic fungi Aspergillus fumigates is the common human saprophyte among the hundreds of species *A. terreus*, *A. flavus*, and *A. nidulans*. They are heat resistant and can survive wide range of temperatures. They are readily demonstrated by fungal staining like GMS and PAS stains. Hundreds o f species have been identified. Commoner ones are the three species: flavus, fumigatus, niger. Temperature of 14° to 50°C is suitable for survival of the fungus and more so with in the range of body temperatuire.

PATHOGENESIS

Man gets infected once he is exposed to the wind of spores. Once the inspired diameter is less than 2.5 microns, it makes them fit into alveoli where they sprout and sporulate resulting in mycelia producing complex immune reaction leading on to chronic inflammation which is T helper 2 mediated inflammation of mucosa [2]of the airways . During

the persistent stages it may invade and cause invasive destruction .Spore load is not directly proportional to the amount of inflammation, because the spores only triggers the cells of inflammation through cytokines , chemokines but they never invade during the initial stages.

The proinflammatory mediators like interleukin 4RA ,manganese superoxide dismutase, ribosomal proteins ,serine protease play a pivotal role in attracting and recruiting peripheral eosinophilic and monocytic response to the bronchial irritation along with enzyme metalloproteinase. Fungotoxin takes the task of bronchiolar damage and dilatation of airways producing ectatic changes.

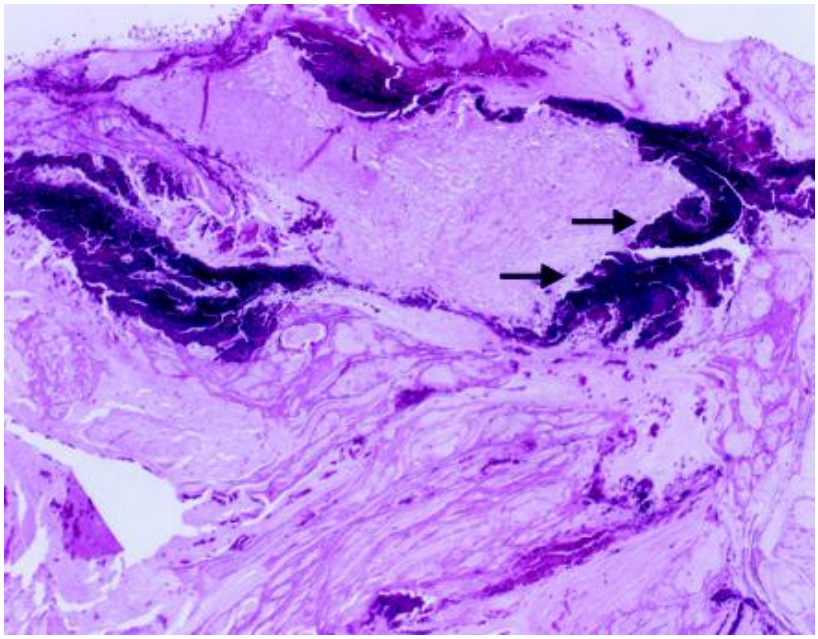


Hyper immunoglobulinemia of IgE type is an evidence of type1 reaction. Type 3 reaction is witnessed by precipitins and the antigen antibody complex causing acute exacerbation. Type 4 reactions occur in chronic diseases with lymphocytic cell predominance in the inflammation. Interleukin 8 levels correlate with neutrophil content of the airway. Mucus secretion causes chronic airway damage. Protease of the fungal origin causes breach in the protective bronchial mucosa allowing aspergillus antigen intrinsically through the mucosa. Other mediator of

aspergillus infection in heat shock protein. Surfactant proteins play a protective role. Forced expiratory minute volume changes in the patient matches with the neutrophil content of bronchial secretion.

PATHOLOGY

Though ABPA never gives concrete evidence of the disease, hypertrophic dilatation of the airway ,goblet cell hyperplasia ,secretions pooled with inflammatory cells consisting of spores ,mycelium, nonseptate fungal element mucosal erosion, and basal layer thickening with interstital septal infiltration may be present in most patients. There may also be airway adaptations and diltation bronchocentric granulomatosis



HPE section mucin deposition in the airways

Signs and symptoms:

- Low grade to refractoy asthma with constellation of symptoms.
- Low grade raise in temperature,
- Cough which is highly productive with golden brown mucosal secretion
- Breathlessness with an audible wheeze, decreased productivity and working capacity. Recurrence and re exacerbation of the similar picture in the form of refractory asthma.
- One should have a high index of suspicion of ABPA in all cases of resistant asthma.

LAB CRITERIA;

1. Raise in absolute peripheral eosinophil count > 1000cells
2. Eosinophils in sputum analysis,(Charcot Leyden crystals, Curschman's spirals ,Creola bodies for asthma) presence of fungal filaments in 10%potassium hydroxide mount.
3. Vanishing lung shadows often homogenous opacities of uupper zone

4. Positive sputum culture for aspergillus species in sabourads dextrose agar medium
5. Skin prick test with instant response of a wheal of more than 4mm within a one quarter of an hour or a second delayed response within 8^{th} hour of the same day .
6. Aspergillus specific raised immunoglobulin E levels
7. Increased serum precipitin levels
8. Central cylindrical bronchiectesis in chronic phase of the disease

Patterson et al stated 5 clinicoradiologial[1] stages

Stages formed along with the laboratory critera of diagnostic significance only and they have less predictive value:

STAGE 1 A known asthmatic and showing features of ABPA with the positive diagnostic criteria. Raised serum Immunoglobulin E levels and raised eosinophil counts with a positve intradermal skin prick test . wheal formation on the back ground of X- RAY changes, in the form of upper and middle lobes opacity such as consolidation. Prednisolone has a crucial role in clinical improvement and symptomatic relief limiting exacerbations

significantly with remarkable x ray clearance and reduction in antibody titres

Stage II— Remission: Reduction of symptoms due to prednisolone therapy, which helps in the persistence of stage I clinical entity for more than 6 months (if the drug is taken with good compliance till the scheduled time)and do not down stage if prednisolone removed from the schedule. Iimmunoglobulins remains at basal values without any rise or fall in titre . X- ray wise complete clearance of opacity not leaving residual shadows.

These group of individuals may remain static or proceed to next step at any point of time

Stage III—Exacerbation: Recurrence of asthma with rising immunoglobulinE titre withn new roentgenographic shadows on chest x ray

Stage IV—Steroid-dependent asthma

Persistence of cough and sputum, with audible rhonchi and infiltrates remaining in chest x ray. Symptoms and blood values of absolute

eosinophil counts and levels of immunoglobulins remains elevated .Inspite of treatment with prednisolone these people detoriate, if prednisolone is removed from the treatment

STAGE 5 End stage: ABPAs who are undiagnosed and simply treated with reliever and controller treatment protocol for asthma ending up in parenchymal and airway destruction bronchiectasis, cavity and fibrosis. Yet treatable still only with prednisolone ,alone only with some amount of response to steroid therapy.

A study conducted by Lee et el commented on reversibility in spirometry i.e. forced expiratory minute volume is > 0.8litres after adequate beta agonist treatment even at stage5.

OTHER CLASSIFICATION-

ABPA further classified as 3 different condition based on symptomatology immunological values [6]

ABPA-S: Patients correlates with the clinical, immunological and blood values fitting into recommended criteria without proximal bronchiectasis

ABPA-CB: Patients expressing other clinical parameters and serum values together with the proximal bronchiectesis

ABPA-CB-ORF: ABPA's together with all the above said features and proximal bronchiectasis together with related x ray findings.They also have other roengtenographic features such as lung fibrosis, scars, bullous changes, cavity formation, and other pleural involvement like effusions and thickening

DIAGNOSIS

ABPA takes place in bronchial asthma patients who are difficult to treat with conventional protocols and also in mucociliary dysfunction involving CFTR gene mutation. Difficult to treat asthma inclusive of possible symptomatolgy, x ray and computed tomographic imaging, serological positivity features with high index of suspicion to coin a patient as Allergic Bronchopulmonary aspergillosis. Fungal growth in culture media of airway secretion can be carried out.

. Atleast a collection of 5 essential features included in the criterion should be present to label a patient as allergic bronchopulmonary aspergillosis.8 Eligibilty features of clinical serological and x ray finding

should be present Are found but among those features some of them are mandatory and few of them were not found and nonmandatory

. The nonmandatory features listed to frame the diagnosis are like, lung opacity and fleeting and vanishing shifting shadows or rised absolute eosinophil count are mostly found only during exacaerbation and initial stage 1 intensive phases of allergic bronchopulmonary aspergillosis only bronchiectasis, affecting the mere proximal segmental bronchi is a concrete evidence of the disease which is uniformly not seen in ABPAs while labelling the patient as allergic bronchopulmonary aspergillosis or during subsequent visits when the patient is under monitor and surveillance.

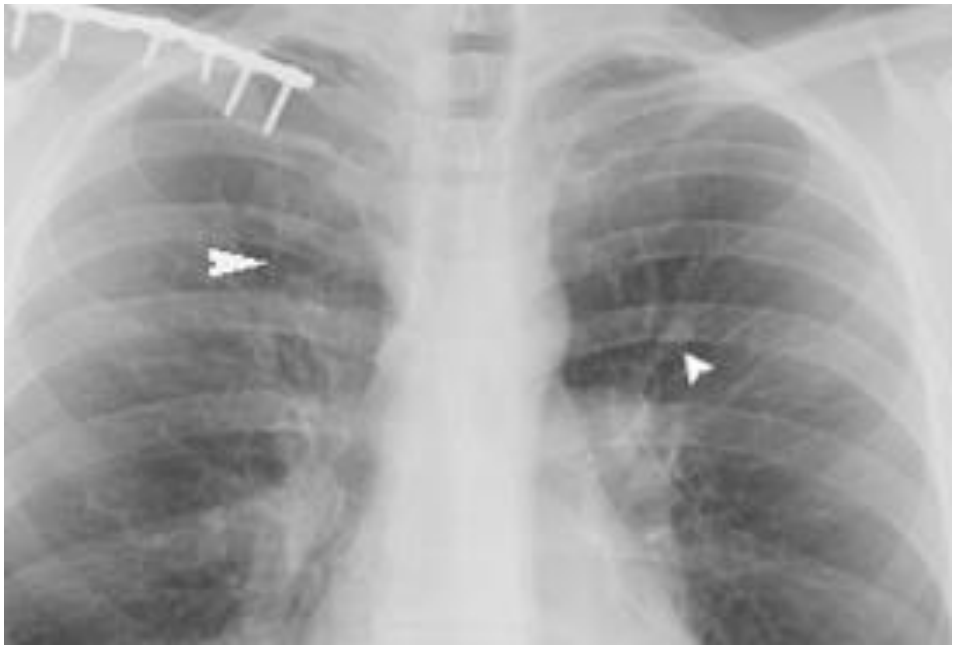
It is difficult to distinguish these patients from cystic fibrosis whicn presents with similar clinical , radiological , immunological features and upper lobe bronchiectasis.(46,48)

Of late, the Cystic Fibrosis Foundation framed a new methodology for differentiating aspergillosis from those patients:49

1. Worsening of symptomatology (cough with sputum, ronchi , restricted Working performance and reduced lung capacity)
2. Type 1 hypersensitivity to *Aspergillus species*
3. Rised immunoglobin E concentration titre with definite cut off

4. Precipitin test positive for aspergillus species
5. Radiological changes like opacities, mucus plugs or ill defined radiographic pictures not related to roentgenographic findings in aspergillosis may be taken as initial findings. The findings in late stages may be the consequence of the recurrent infections during initial stages predictive of persisstant destruction of the airways or parenchyma

EARLY CHANGES: The initial changes affects the parenchyma and is seen in in almost 80-90% of ABPAs as obscure homogenous roentgenographic opacity with no substantial loss in of lung parenchymal contour, but confined or extensive lesion. Any area of the lung parenchyma can be affected but the common part of the lung routinely affected are upper zones.(54) Upper zone opacities disappear once the patient coughs out the secretion. This is a classical and remarkable feature. Sometimes shadows may be shifted to remaining lobes so called migratory shadows. Some of them heal with persistent mucus plug identified as 'ring shadows'. Plugging of the the epithelial mucus secretion that blocks the lumen produces uniform shadows in a skiagram.



X-ray showing early aspergillosis: Lung infiltrates

Proximal airway changes occur in 50-70% initial periods of aspergillosis of ABPA. Chest roentgenographic picture shows tramtrack, parallel line (intact or dilated proximal airways) “toothpaste” and gloved digits (indicates airways thick tenacious secretion). Tramtrack opacity are the hypertrophied bronchial wall with a near normal luminal diameter. Parallel lines are the wall of both hypertrophied and ecstatic permanently dilated airways with increase transluminal diameter Ring shadows are of airways are also due the same reason.

Bronchoscopy and Broncheoalveolar lavage with suction removal of the tenacious secretion results in x ray clearance of the opacities such as tramtrack appearance and other evanescent opacities .In 15-30% of

aspergillosis patients , mucoid plugging of the proximal airway seen . If it is affected by mucoid plugging of large bronchus and spreads into the 3rd 4th order airway toothpaste opacity is formed but if it sequentially affects the 2nd order bronchi it forms the gloved finger markings which are bronchiolar radio opacities 2-3 cm long and 5-8 cm wide branching distally from the hilum and filled with inflammatory exudates producing thick tenacious secretion . The opacity at the hilum seen in about 40% asthmatic days of Aspergillosis resembles peribronchial lymphadenopathy at the hilum, other resemblances are cavity, fluid shadow, widespread nodular opacities involving all the lobes and watershed areas. Emphesematous bulla changes may rarely be seen with the incidence of less than five percent while other changes range from ten to twenty percent in incidence.(55).

LATE CHANGES –Late pictures are due to recurrent infection recurrent and inflammation. The late changes are manifested as fibrosis sparing the middle and lower zones affecting other areas. Fibrosis, fibrocavity formation, bulla rupturing into the pleura occurrence are literally terminal .53,54,56

Abnormal persistant permanent and irreversible dilatation of proximal airways are hallmark of aspergillosis.

CT CHEST showing invasive aspergillosis

But it differs in one way from the other diseases by destroying earlier generation of bronchi in contrast to otherway involving terminal bronchioles. High resolution computed tomography is the best diagnostic aid in picking up the central bronchiectasis , reticulonodular pattern are other findings madeout [5]

SPIROMETRY-

Forced Expiratory minute Volume, FVC, Peak Expiratoy Flow rate and diffusion lung capacities were not only applicable in selecting and identifying the cases but also for the prognostic prediction and reduction in above parameters is noted in resistant and steroid dependent stages of allergic bronchopulmonary aspergillosis . The reversibility of obstruction> 15 % after adequate bronchodiltation, even in stage 4 disease and reversibility of more than 0.8 % has a good prognostic value[6].Pulmonary function test shows both obstructive and restrictive pattern at the time of asthmatic attacks

Severity of decline in FEV1/FVC ratio is patient dependent variable.(59,60,61).Wide range of PFT variation is seen in aspergillosis starting from static function to worsening and rapid derangement of lung function and as said earlier , spore colonisation load and sputum eosinophilia load is not directly proportionate to change in spirometric declination of the patients.

GUIDELINES TO DIAGNOSE ALLERIC BRONCHO-PULMONARY ASPERGILLOSIS IN AN ASTHMATIC PATIENT

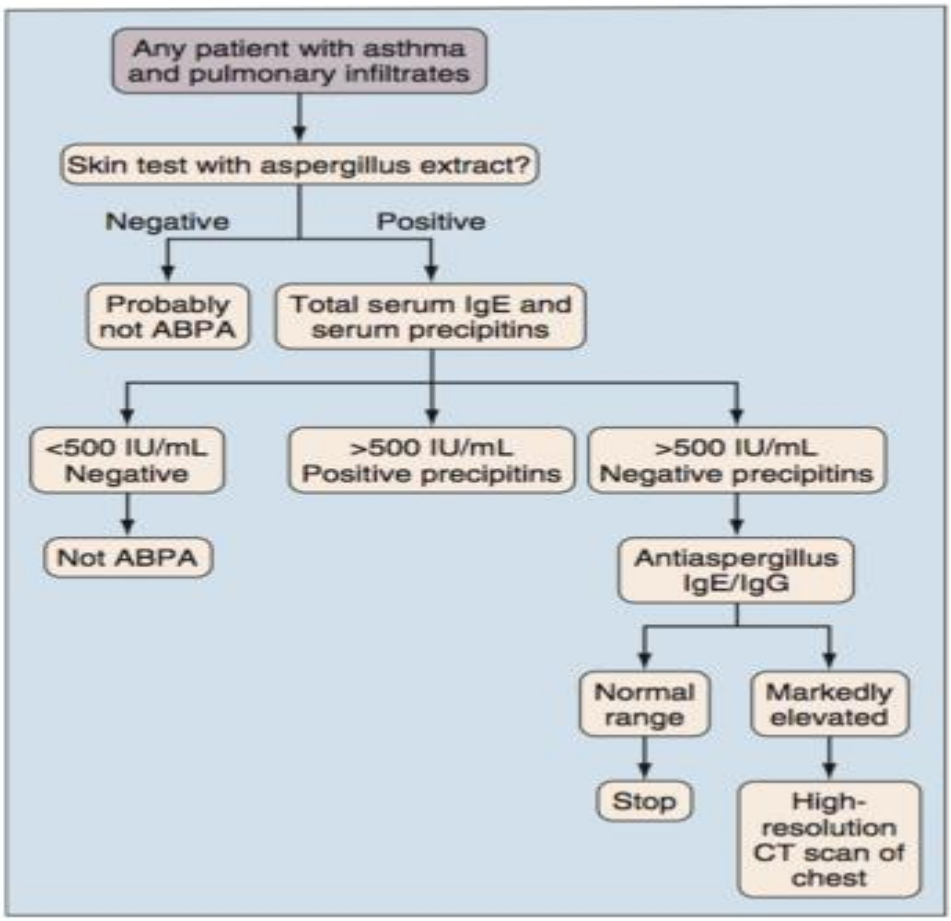
Whenever patient comes to us with the history or features of bronchial asthma , difficult and refractory to treatment with frequent exacerbations or poorly controlled asthma with or without radiographic evidence of consolidation or collapse , look for the underlying possibility of a trigger factor on the back ground of the patient being an atopy suspect for allergic bronchopulmonary aspergillosis.

Do a pulmonary function test to assess the reversibility and pattern of the disease. Do a screening skin prick test to detect a wheal of more than 3mm to predict the tendency to produce increased IgE.

Assess the peripheral eosinophil count and serum IgE level if significant levels were found.

Do a high resolution computed tomography to look for CENTRAL BRONCHIECTESIS.

Serial IgE levels can be used as a tool for follow up.



Aims of the therapy

a. Identify and treat the cases at a early stage to prevent recurrent attack
b. sterilize the airways and mucosal secretion against this monomorphic fungus to prevent further attacks and relapse
c. relief from the recurrent attacks of ABPA like cough, breathlessness, wheezin,

d. to arrest the stage wise progression of disease and prevent permanent structural and functional damage like central bronchiectesis

COMPONENTS OF TREATMENT

a. Oral prednisolone to fasten relief , curb inflammation and to stop ongoing process of airway damage
b. Antimycotic therpy to sterilize the fungal colonies in the sputum and the airways , mainly Itraconazole.
c. Bronchodilators and the airway hygeine

STEROID THERAPY

Oral prednisolone therpy has become the sheet anchor during the initial phases of the disease to relieve the symptom caused by injury due to inflammatory cytokines most efficient in decreasing the airway hyper responsiveness and there by decreasing the rhonchi and accelerating the x ray clearence It is most efficient by decreasing the blood eosinophil level and serum immunoglobulin E level.

Oral PREDNISOLONE 0.5 mg/kg/24hr during initial 14 days,tapered with same dose on alternate days[6] for atleast 21 weeks is

the initial treatment. The dose is further reduced till immunoglobulin levels becomes static , parallelly watching over the relief of the symptoms and a good radiological clearance of the disease there by preventing exacerbation and maintaining the patient on remission phase and reversal of spirometric derangements thereby increasing working capacity and lung compliance.63

The lung function tests recommended for asthma patients must also be performed which may show decreased lung volume, diffusion capacity or is the nature of attack dependent.[23][17]

STEVENS et el studied the methodolgy of tapering the steroid level and its adverse effects like glucose intolerance and adrenal suppression taking into considerstion dosage schedule.

Prolonged predniosolone therapy is not adviced . If the patient is free of attacks for about 24 weeks he is in stage 2, the remission stage. Stage 4 patients may have recurrent attacks and he has to be put on maintainence prednisolone therapy to prevent relapse and they will worsen if they were taken off steroid therapy. Patients in stage 5 will have poorer prognosis with bad structural damage predisposing repeated secondary infection gram negative sepsis and not so responsive to steroid therapy.

ANTIFUNGAL THERAPY

So many broad spectrum antifungal have been tried and failed but for their side effects (64). Inspite of the other side-effects the antifungal agent, Itraconazole is found to have major role in allergic bronchopulmoary aspergillosis . A four month drug trial made showed impressive results in steroid responsive asthma with end results in the form of following criteria with almost half the dose reduction of prednisone results in

1) ¼ th decrease in Immunoglobilin concentration a
2) tleast ¼ increase in working capacity
3) an improvement of at least 25% in exercise tolerance or pulmonary-function tests

OMALIZUMAB :

HELE SIM PARK et al studied role of omalizumab in steroid responsive Allergic Bronchopulmonary Aspergilllosis as an add on therapy (Cochrane Airways Group Asthma Trials Register) .There was a good radiological and mycological clearance in their study (66). omalizumab prevents bronchial remodeling when administered along with the oral

steroids. Adrenal suppression associated with steroid therapy is checked by the co administration of itraconazole 200 mg/od .Treatment for a period of 4 months has shown good response. No tachyphylaxis was noted on continued treatment . Voricoazole and posconazoles has no superiority over itracanazole in the treatment of ABPA. Omalizumab (Anti IGE monoclonal antibody) is also effective in refractory ABPA.

BRONCHODILATORS-

Inhalational broncho dilators has additive role in the treatment of ABPA . Bronchoscopy and bronchioalveolar lavage can relieve the obstruction and can relieve the passive collapse.

ROLE OF ADULT VACCINES AND ANTIBIOTICS

Pneumococcal and human influenza vaccine should be administered in all patients receiving prolonged immunosuppressive therapy. Anti pseudomonal and drugs against atypical bacteria have a definitive role in the treatment .

GENOMIC LINKS

People having polymorphisms of Human Leukocyte antigen-DR and –DQ of type 2 major histocompatibility complex , Interleukin 4 and-

10-1082GA mutation and surfactant protein A2 mutation are predisposed to develop ABPA.

The hereditary links and subsequent rise in single cell lineage aids in demarcating highly susceptible individuals . Omalizumab can be successfully used in this patients .

Allergic bronchopulmonary aspergillosis disease is first reported in Britain and 10 years later in US thereafter significant mortality and morbidity studies have been recognised from various datas that its invasive terminal pathology, these molds are survivors in the Middlewest and eastern coastal areas. Aspergillus spores are common in indoors and outdoors. Universely spread without any restriction Aspergillus species are thermotolerant growing at 15° to 53°C temperatures and particularly grows well at 37° to 40°C which allows for sporulation in human bronchi. Septated hyphae of A. fumigatus are 8 to 11 µm in diameter with branching at 45° angles. Hyphae may be demonstrated in sputum, mucus plugs or sinus debris with Gomori methenamine-silver or periodic acid-Schiff stains.

Aspergillosis may play a role in cystic fibrosis and asthma. Helper T- cells directed against antigen of the monomorphic fungal elements was demonstrated by ALAN P KNUTSEN in patients with cystic fibrosis and

asthma. The fungal antigens may trigger the inflammatory response that results in clinical detoriation..Other diseases caused by this mycoses are invasive fugal ball inside the cavity, madhura foot ,3.1.

ABPA AND ASTHMA:

DENNING AND WARDLAWS et al. in their study of atopic asthma found Hyper IgE and its heightened hypersensitivity to fungal spores in the study population. The presence of ABPA was related to persistent intensive high grade asthma with recurrent attacks and rapid decline in lung volumes and capacity .

Other causes of fungal allergic mycoses was by penicilium marnefi ,cladosporium ,candida and Pseudoallecheria boydi .19–23

Diagnosis of ABPA relies on the demonstration of fungal mycelium and peripheral blood esinophilia (>thousand cells per millimeter cube). Because most of the normal individuals may also harbour aspergillus in their respiratory tract as a part of colonization , demonstration of sputum fungal mycelium alone is not diagnostic of ABPA. Growing of sputum colonies in SDA agar is not considered as a diagnostic criteria (19 - 25).

In contrast to Madura mycosis , elevated serum precipitin levels cannot be considered as diagnostic of ABPA.

Hemmann et al. [24] studied levels of IgE antibody against recombinant A.fumigatus Asp f1, Asp f3, Asp f4, and Asp f6 antigens. They found out Immunoglobulin E directed against Asp f4 and Asp f6 was remakably unique for aspergillosis.

In Korean study, patient selection was based on Greenberger criteria and intradermal test done as a screening test with mycoserogical values. In this study he compared ABPA patients with pre existing TB sequelae with controls and found poorer prognosis in those patients and ANTI IgE therapy is alternate to prednisolone in this group.

Patients known to have recurrent attacks with acute asthmatic ABPAs declines withsevere disability ,endangering acute attacks than their fellow asthma patients . They need more patient oriented therapies in addition to regular protocols like controllers and relievers like long acting beta agonist, LAMA, IHC .anti IgE ,azithromycin, cholecalciferol supplements, avoidance of pollutants and overcrowding, Immunisation stage oriented treatment, use of crisis busters are rescues reserved for fulminant asthmatics.

A study in American journal of respiratory and critical care medicine states that immunoglobun E sensitivity of Aspergillus fumigatus correlates with dampened spirometric function in asthmatics.

Patients with high immmunoglobulin load have decreased spirometric value mainly Forced Expiratory minute volume(FEV1) ranges from around 80% in resistant cases, around 60% in hyerimmmune IgE 50 to 60% in cystic fibrosis and <35% in bronchiectasis.[1]

ELIAS MIR et al studied an analysis relating two spectrum Allergic bronchopulmonary aspergillosis and chronic bronchitis/emphysema. Both of these obstructive airway disease has correlative overlapping pathophysiology except for postbronchodilators reversibility which is more in asthmatics than in emphysema and chronic bronchitis with the history of smoking. The study was noticed by a case scenario where a COPD patient found to have allergic bronchopulmonary aspergillosis fulfifilling criteria like skin prick test and other serological test but the reversibility of the patient lung function was not so significant owing to the structural damage in the airways and parenchyma noticed. Patient initially came with respiratory symptom got improved clinically, the author concluded the study by stating that some shared pathobiology exist in this condition and that could be genomically related by familial hyperresponsiveness.

DANNI .S.ZANDER et al in his study compared statistical datas for allergic bronchopulmonary aspergillosis and patients with CFTR hereditary

mutation link between both the disease, in CF, defective dyenin arm in the mucosal lining incapacitates the patient to clear his mucus collection there by resulting in secondary infection. Persistence of inhaled spores triggering immunopathogenesis of the disease[4] dealt with the underawareness of the disease and the feasibility of identifying the case is only possible if the consultant has the idea about the profile of the disease, otherwise case will be submerged with the other asthma groups . Author of this article also enumerates the various manifestation and its clinical manifestation caused by A.fumigatus like ABPA, consolidation , invasive parenchymal and airway disease spectrum with the end results of Aspergilloma, Brochiectesis and so on, leading on to blood tinged sputum , desaturation and respiratory failure. Hypersensitivity plays a major role in this disease with the risk factors, like atopy, asthma, pulmonary TB sequelae, primary immunodeficiency disease along with retroviral disease and both immunocompetent and immunosuppressed individual are at risk of aspergillus series of disease.

AGARWAL R et al included hereditary link with interleukins, toll like receptors, tumor necrosis alpha ,human leukocyte antigen and major histocompatibility complex , alternate complement pathway has been mentioned especially Mannose binding lectin dependent pathway and

[5] the author has also dealt with late reaction to intradermal test as a non essential criteria. The treatment schedule role of prednisolone, azole group of antimycotic agents , biologicals like omalizumab in the treatment and bronchial hygiene has a specific mention; bronchial thermoplasty has a role, whose prognosis and complications are well dealt with statistical evidences.

Cochrane et al G A T Register[15] there was a good radiological and mycological clearance obtained with Itraconazole treatment by preventing bronchial remodeling. The prednisolone induced adrenalgland suppressive effect of corticosteroid therapy is checked by the co administration of itraconazole. It also acts by clearing the airways making the airways mold free by preventing mycelia formation and destroying conidiophores if given over 4 months. It has mycelia sterilizing effect and good response immunomodulation with no tachyphylaxis or drug resistance on continued treatment. Voricoazole and Posconazoles gives no extra benefits.

TILLIE –LEBLON et al in his study – mentioned about the universal nature of the spore and link CD 4 helper cells in pathogenesis. Mention about the cultural charecteristics in SDA media and a special mention about GROCCOT stain and conidiospore which triggers both cell and

antibody mediated chemotaxis; mold load is not a deciding factor in the severity of the disease[9]

RADIN et al studied about the Host Factors comprising Gel and Coomb hypersensitivity response forms the main deciding factors.

GIBSON et al links the presence of chemotactic interleukin and phagocyte load and exudative sputum has proportionately worsened disease spectrum.

Radi et al –VLA-4, CCR-3 as a special role in chemotaxis [1] discussed the pathogenesis of the disease along with the other novel chemokine and metalloprotien lysis

GIBBSON et al studies the incidence of ABPA in the pediatric age group but declines to state that though allergen plays a main role it is a disease of middle aged [10]. There is immune tolerance and development of repeated sensization in the middle age group because of the chronic exposure.

PATERSON AND GREENBERGER – analysed various symptomatology and came out with a classification and staging as five various groups facilitating treatment schedule and the stages are not static for a given patient it may down stage without treatment or remain static and undergo remission

LEE et al shows reversibility of bronchospasm after adequate treatment and studied about the foced expiratory minute volume improvement even in late stages of the disease in his trials [4]

Malo eval et al studied about the link between the asthma and Aspergillosis in respect to proximal bronchiectasis. Incidence in asthma is around half of the central bronchiectasis about 31 % in ABPA.

NEELD GOODMAN et al using computerised tomography incidence ectatic changes in asthma and it is found that correlation is found in 2/3 rd of the ABPA patients with this terminal airway disease association.

ANGUS et al studied the incidence of passive collapse using HRCT and came out with incidence of 4% in allergic bronchopulmonary aspergillosis [8] other changes like pnuemothorax and calcification is seen in insignificant numbers

REIFF et al compared the peripheral location in few cases of bronchiectesis. It is insignificant in number and not pathognomonic of allergic bronchopulmonary aspergillosis when compared to proximal air way disease which is the hall mark finding.

WARK PA et al – worked on antimycotic treatment; in certain cases they have immune modulatory effect besides cutting down fungal

reproductory and budding rate . He studied a meta-analysis of two groups using itraconazole and came out with the successful statistical values.

MCCARTHI et al [16] studied the relationship with prolonged inhalation of spores in relation to disease severity index the result was not so significant since antigen is more necessary than antigenic load by itself.

STEVENS et al [17] studied about the toxic effects of antimycotic azoles and confirmed the safety margin with which it can be given for months without any noted side effect

MIDDLETON, CAPE BELL et al studied about the maximum[18] oral prednisolone for long duration never benefits acute attacks of aspergillosis or asthmatic attacks, inferring that there are other factors like repeated exposure may trigger complement activation[20]thus the adjuvant use of [19]antimycotic therapy has its own value in extending cure rate of the patients with ABPA.

NEEDGOODMAN et al studied the usefulness of high resolution CT in detecting minor pathology of the respiratory system [21];it founded out several minor details it is the investigation of choice in bronchiectasis.

MACARTHY GREENBERGER et al studied about the usefulness of the skin prick test immediate wheal is only common comparing with the

late type 4 hyper sensitivity reaction which is seen in less than 1/3rd of the patients. The test is predictive in all ABPA cases.

RICKETI GREENBERGER et al studied about the absolute eosinophil count. Peripheral Eosinophil count has a diagnostic value together with the sputum eosinophil count. It is the sensitive test along with chromatographic line representation of antigen antibody response and raised immunoglobulin E and G titre will depict the severity of the disease and the levels can be used for follow up during remission and exacerbation.

COMPLICATIONS AND PROGNOSTIC PREDICTORS

There are only retrospective studies and the population oriented prospective trials are more expected and yet to come to predict the prognostic factors in this disease . A few number of case ends with scarring and fibrosis of the lung parenchyma and very few progress to right heart disease secondary to lung pathology and rest of the diseased group is nonprogresive in lung performance and working capacity even for a decade or more.

MAL et al studied and compared a five years Lung function in asthmatic with Allergic Broncho Pulmonary Aspergillosis and without

aspergillosis .The later group was performed well with good and adequate lung capacity than the former group with declining PEFR and superimposed restrictive along with the obstructive pattern of the aspergillosis. Patients with structural lung disease worsen more earlier than the serological ABPA groups. At the end several inference were obtained, Allergic Broncho pulmonary aspergillosis is not unusual in chronic airway disease inspite of high prevalence this disease is diagnosed only in late stage of the disease and supportive treatment are atmost nessesary to culminate the progression of the disease . In an Asthmatic with a chronic and refractory course, suspect aspergillosis and treat appropriately according to their respective stages in which the patient land to us there by doing justice to the long term asthma groups.

FEW RADIOLOGICAL REMINDERS OF ASPERGILLOSIS

- Proximal Bronchiectasis
- Migratory lobar pneumonia
- Ring opacity
- Double line opacity
- Lobar scarring
- Tooth paste like opacity

- Honey Combing like pattern
- Tram track opacity
- Collapse
- Aspergilloma with air crescent sign
- Finger like opacity
- Ground glass opacity
- Tree in bud appearance
- Reticulonodular pattern

are the major x ray findings seen so far.

Nevertheless one should not forget an absolutely normal chest x ray never rules out the disease which is the rule of thumb what we studied in asthma patients with or without ABPA.

MEERK et al en listed the complications of therapy with prolonged immunosuppression.

immunosuppresion and its complications

- Secondary bacterial or pneumocytis jeroveci infection
- Adrenal axis suppression
- Fungal infections
- Gastero esophageal relux disease
- Drug tolerance(rare)

MATERIALS AND METHODS

It was felt that we need to study a large group of asthmatic population with the major aims of diagnosing allergic bronchopulmonary aspergillosis in the study group. Patients coming to the Medical OPD, emergency wards and asthma clinic of Rajiv Gandhi Goverentment General hospial for Asthma related problems, atopy and allegic rhinitis with frequent exacerbation are enrolled into the study. This hospital is a Tertiary care centre for the urban and rural population in an around Chennai and neighbouring states.

This is a programme comprising of identification, staging, treatment and follow up of allergic bronchopulmonary aspergillosis among the patients found to have resistant to conventional treatment. A previous Indian statistics, done using Rosenbergs criteria, among 651 pateints, showed that 338 found to have positivity(52%) with 89 proven by Rosenbergs criteria; since the entity was not focused completely to highlight underprevalence, hence the study was conducted in patients attending asthma clinic medical OPD and wards were taken as subjects with sample size of 100 patients in different age groups, sex, with or without family history, smoking and atopy history after subjecting patient into pulmonary function test. With all these in mind a sample size of 100

patients was helpful in confidently conducting the study and priming them with details and help them addressing the questions in the study.

Inclusion criteria**:**

1. Patients with uncontrolled bronchial asthma.
2. Patients with frequent asthma exacerbation.
3. Patient having difficulty in tapering inhalational steroids.

Exclusion Criteria :

1. Severely ill patients coexisting other respiratory diseases
2. Patients with disorientation and unable to take part in the investigations.

Study Conduct

Number of patients:

100

Methodology

1. Obtaining informed written consent from the eligible patients or their legal representatives.
2. Filling up of the semi structured questionnaire by interviewing the patient or his attender.
3. Stratification of Bronchial asthma and Allergic Bronchopulmonary Aspergillosis patients according to guidelines .
4. Laboratory investigations – Complete Blood Count, total serum IgE Concentration.
5. Chest X Ray ,
6. Absolute Eosinophil Count, Pulmonary function test, KOH Mount, and Skin Prick Test
7. Initially patients will be screened according to inclusion and exclusion criteria and the patients will be assessed for the risk factors of allergic bronchopulmonary aspergillosis
8. Those patients who got admitted for asthma exacerbation and Steroid dependent asthma will be followed up
9. Patients will be followed up for a period of six months first at the end of 15 days then at 30 days and later at monthly intervals for a period of six months.

10. The patients will be consulted regarding any re admission for respiratory events and other illnesses.
11. Statistical analysis of the collected data.

Statistical Analysis

Descriptive statistics would be done appropriately using patient characteristics and other data collected in the study.

Statistical Methods

SPSS

Epi INFO

ANOVA

CHI SQUARE

Results and observations

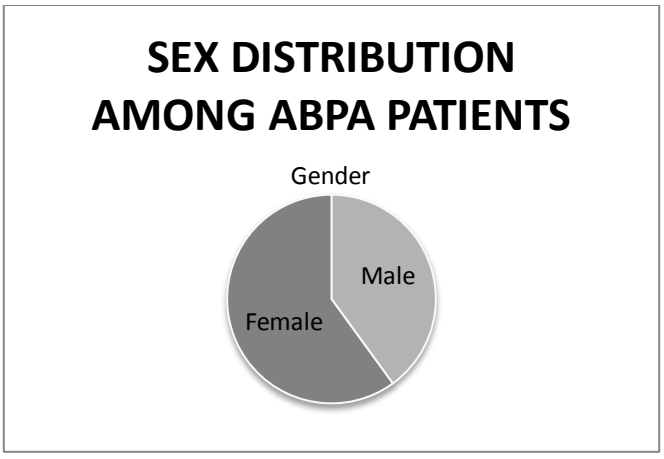
Population characteristics:

Among the 100 patients included in the study after fulfilling inclusion criteria the following results were obtained. 40 were male asthmatics and 60 were female asthmatics.

Using criteria, allergic bronchopulmonary aspergillosis was diagnosed in 19 patients out of 100 refractory asthmatics.among them number of females were 11 (57.9 %) among the total ABPAs).total number of male ABPAs were 8(42.1%)

Gender	Number of patients	No. Of patients with ABPA	%of ABPA patients
Male	40	8	42.1%
Female	60	11	57.9%

P value= 0.100, statistically not significant.

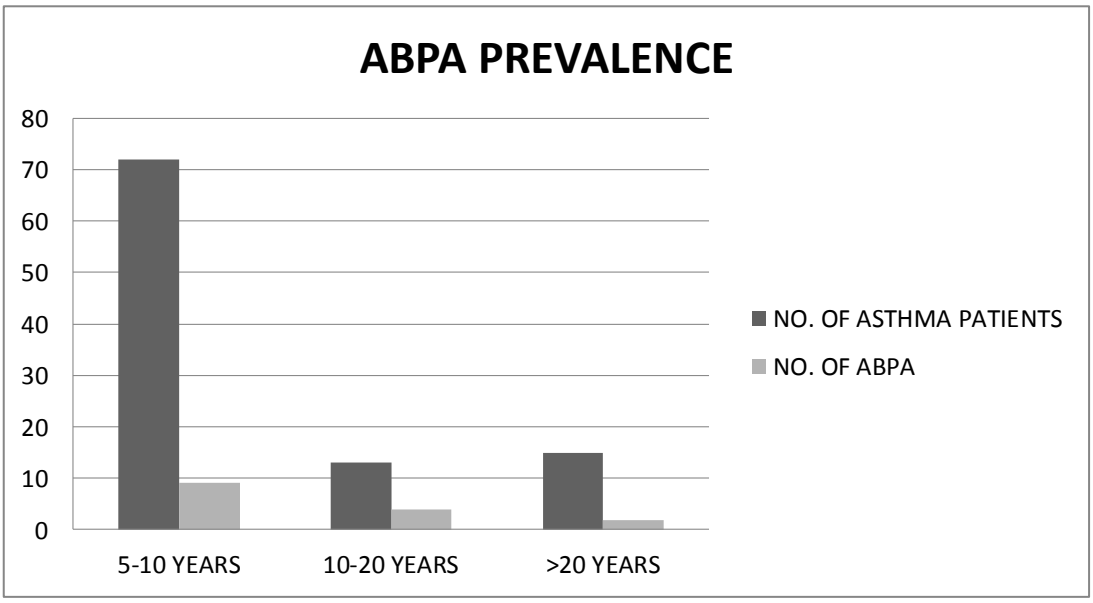


Comparative statistics of the ABPA positive and ABPA negative individuals

List of variables	ABPA positive(n=19)	ABPA negative(n=81)
Number of patients	19	81
Mean age	34.421±10.90	36.67±9.92
Male:female	8:11	32:49
Duration of asthma	15.2±10.2	17.34±9.60
Family history(no.)	17	33
Skin prick test positive	17	0
Mean absolute eosinophil count	1322.73±458.99	288.13
Mean IgE levels	2245±458.99	694.41±567.07
Chest x ray	Normal:12, abnormal:7	Normal
HRCT chest	Normal:12 abnormal:7	Normal
Sputum KOH mount	10	0
H/o atopy	14	12
Mean pretreatment exacerbation	3.52±1.17	0.90±0.63
Mean spo_2	95±3	98±1
Mean post treatment exacerbation	0.94±0.70	0.85±0.03
Mean FEV_1/FVC	0.73±0.06	0.85±0.03

Duration of disease:

Duration of asthma in years	No. of ABPA patients	No. of asthma patients
5 to 10	9	72
10 to 20	4	13
>20	6	15



Duration of asthma

Duration of disease	ABPA group(n=19)	Non ABPA group(n=81)
Mean(in years)	15.2	17.34
SD	10.2	9.69

P value = 0.39 not statistically significant

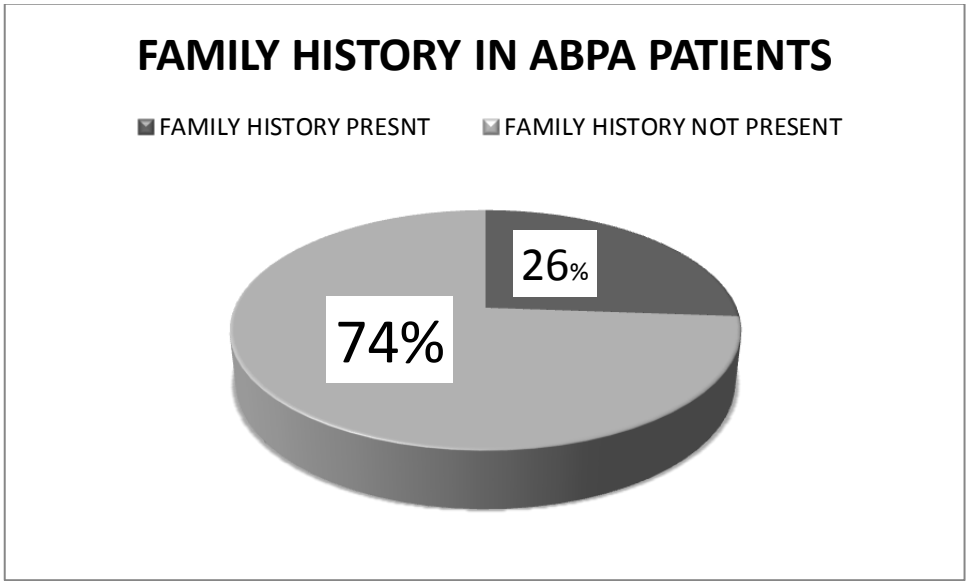
Family history comparison:

Family history	ABPA group(n=19)	Non ABPA group(n=81)
Positive	17	48
Negative	2	33

P value is <0.01 statistically significant

Fisher eact test with CI of 95% by ANOVA method

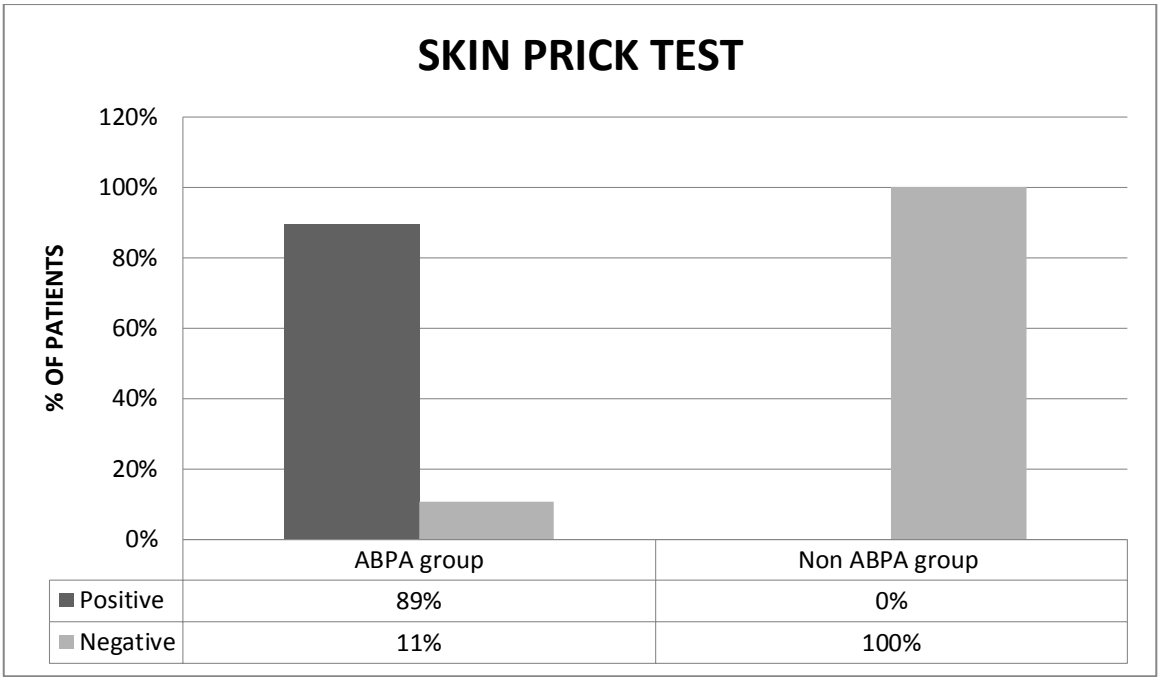
Relative risk for the above data is 4.57



Skin prick test and ABPA:

Out of 19 patients with ABPA, 17 had positive skin prick test.

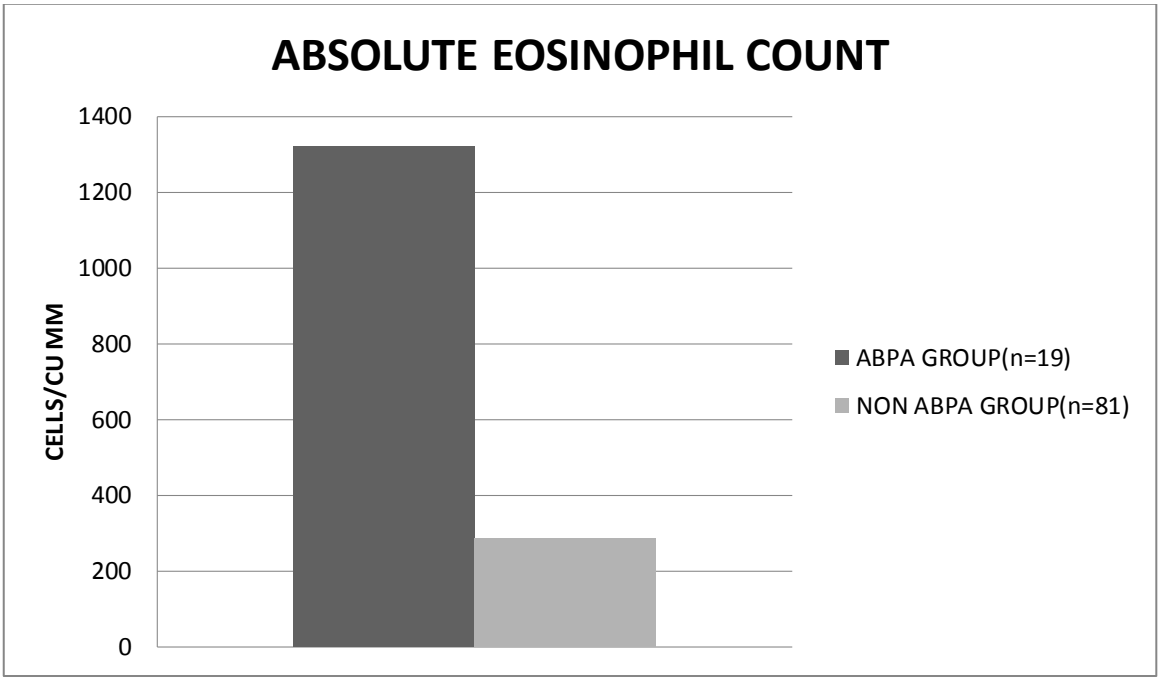
Skin prick test	ABPA group(n=19)	Non ABPA group(n=81)
Positive	17	0
Negative	2	81



P value is 0.0001 statistically very significant

Correlation between absolute eosinophil count

	Absolute eosinophil count(cells/cumm)	
	ABPA group(n=19)	**Non ABPA group(n=81)**
Mean	1322.73	288.135
Sd	458.99	338

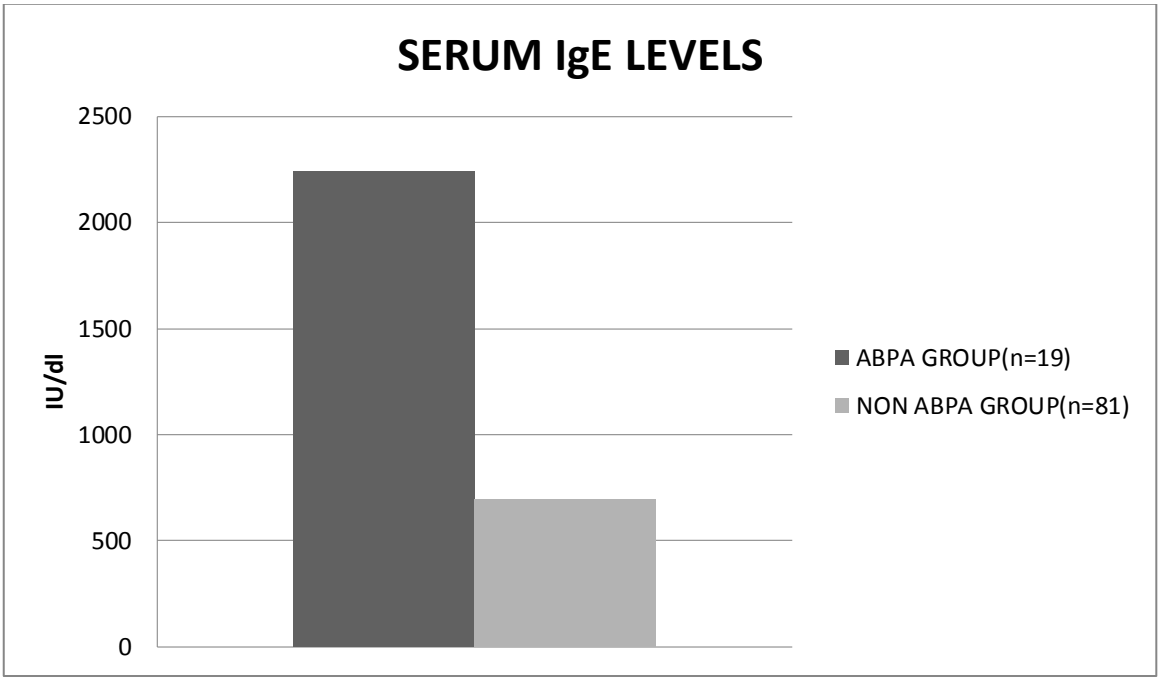


p value is o.ooo1 statistically very significant

Correlation between serum ige levels

	Ige levels(iu/dl)	
	ABPA group(n=19)	**Non ABPA group(n=81)**
Mean	2245	694.41
Sd	482.38	567.01

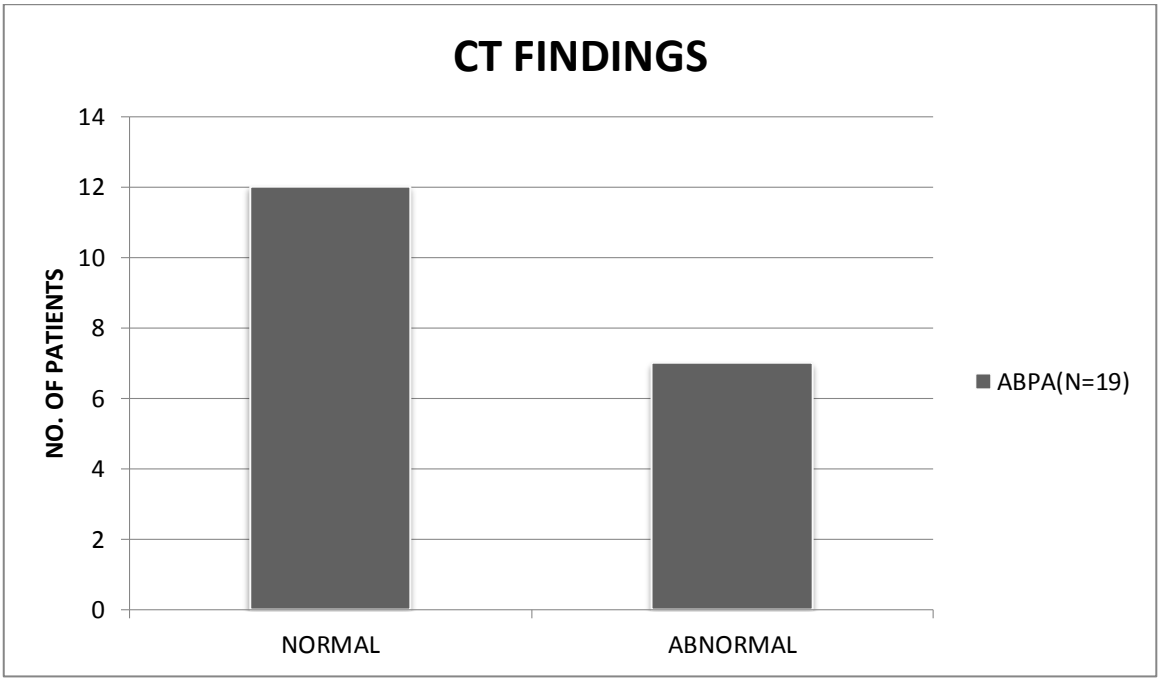
Pvalue <0.0001 statistically very significant



CORRELATION BETWEEN CT FINDING :

CT finding	ABPA(n=19)	Non ABPA(n=81)
Normal	12	81
Abnormal	7	0

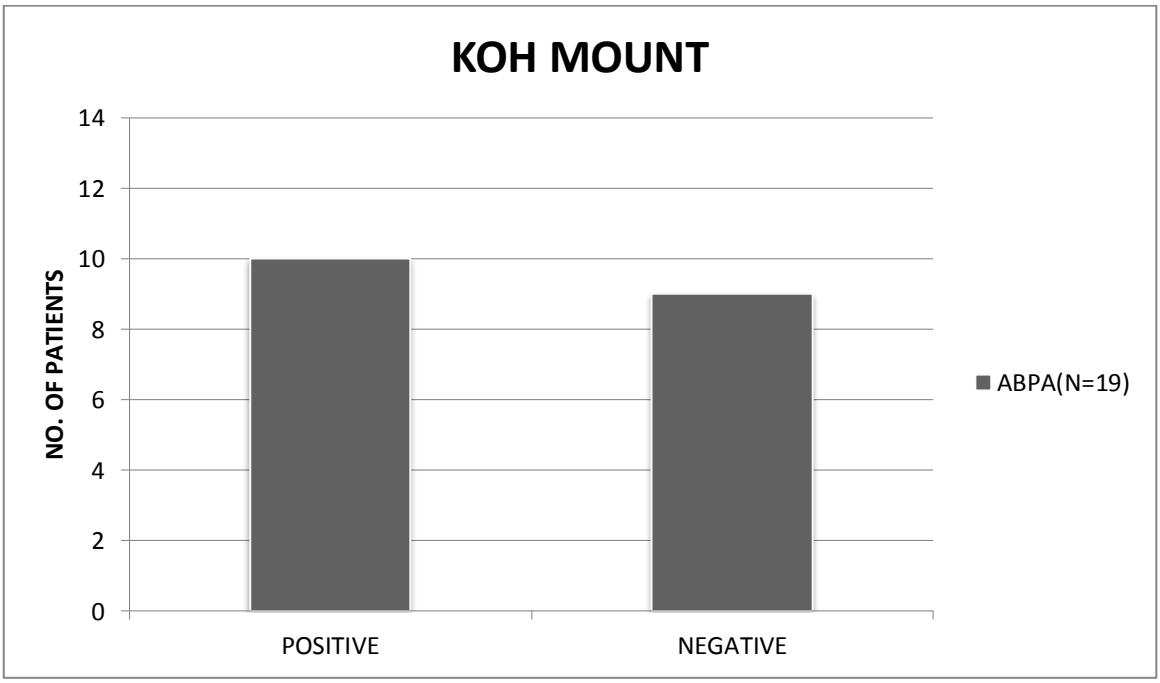
P value <0.0001 inference extremely significant



Correlation between sputum positive for spores in KOH mount

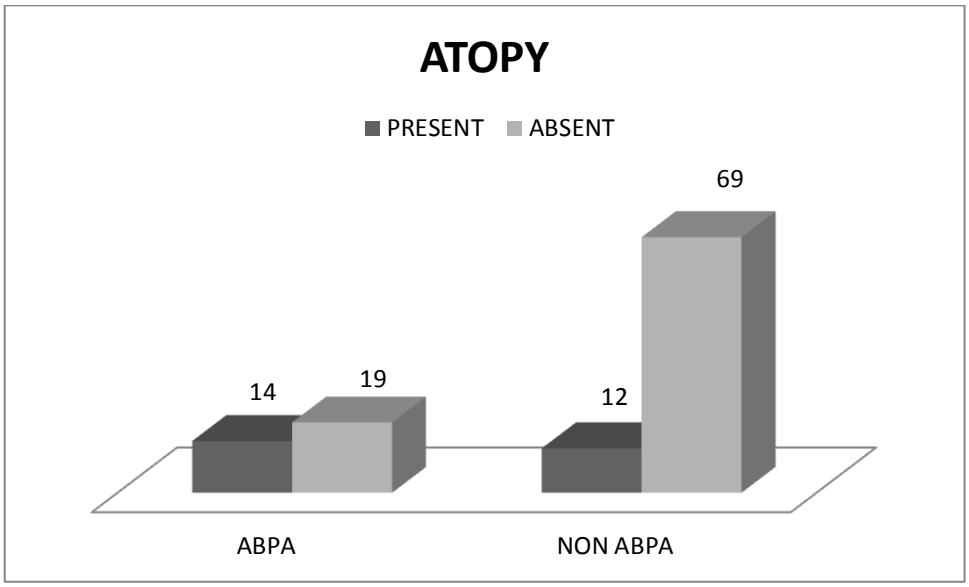
Sputum koh	ABPA(n=19)	Non ABPA(n=81)
Positive	10	0
Negative	9	81

P value<0.0001 is extremely signifcant



Correlation between history of atopy

Atopy	ABPA(n=19)	Non ABPA(n=81)
Present	14	12
Absent	19	69

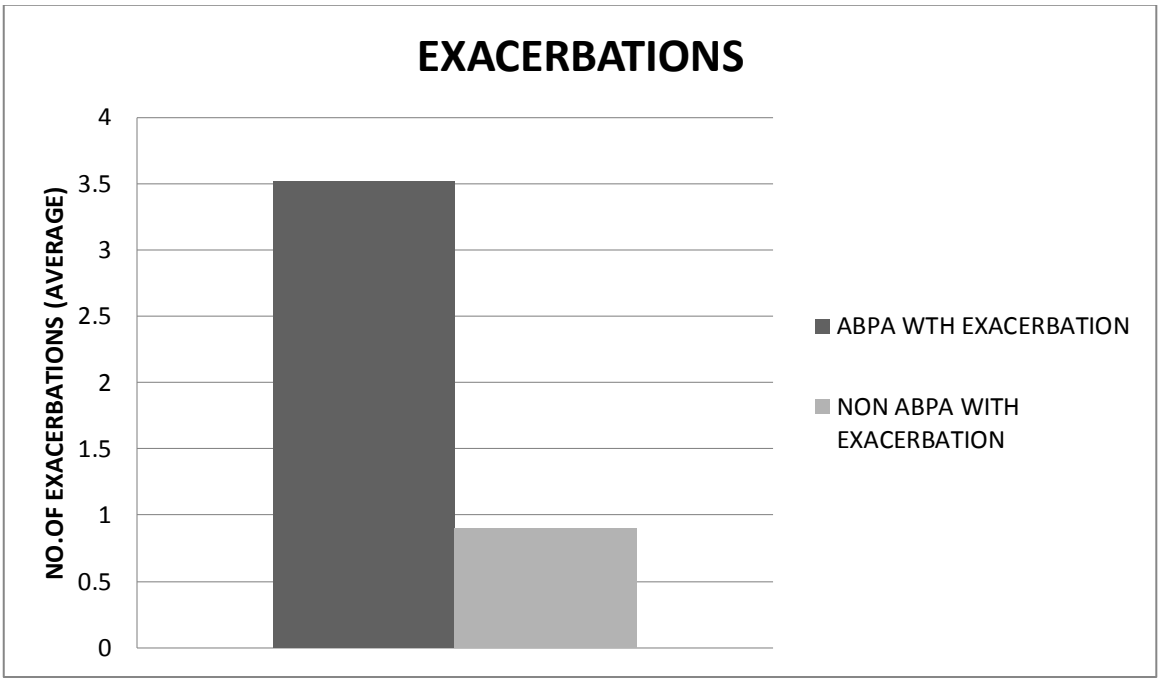


P value is < 0.0001,statistically significant

Correlation between pretreatment exacerbation

	ABPA wth exacerbation	Non ABPA with exacerbation
Average	3.52	0.90
SD	1.17	0.63

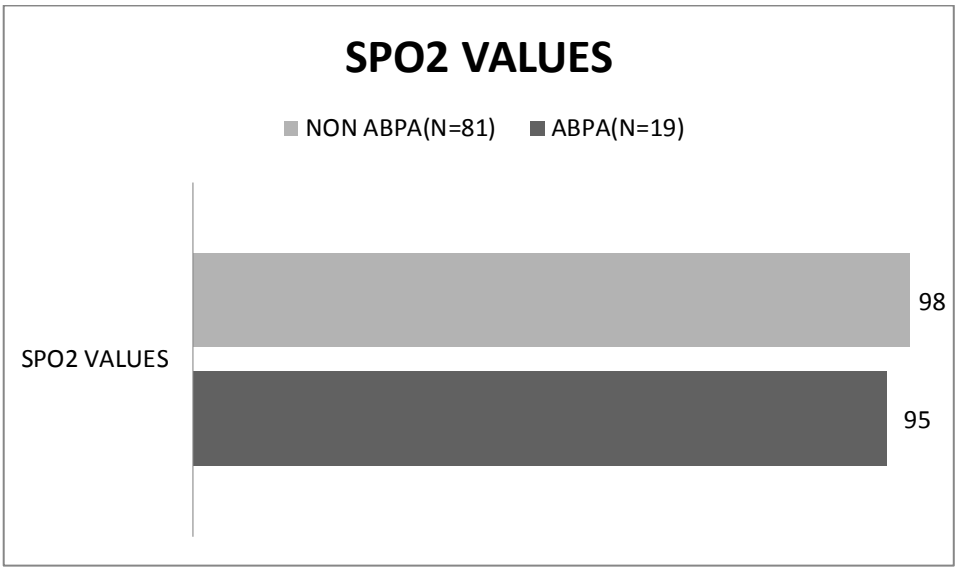
P value <0.0001 inference extremely signficant



CORRELATION BETWEEN SPO2

	ABPA(n=19)	**Non ABPA(n=81)**
Spo2 values	95±3	98±1

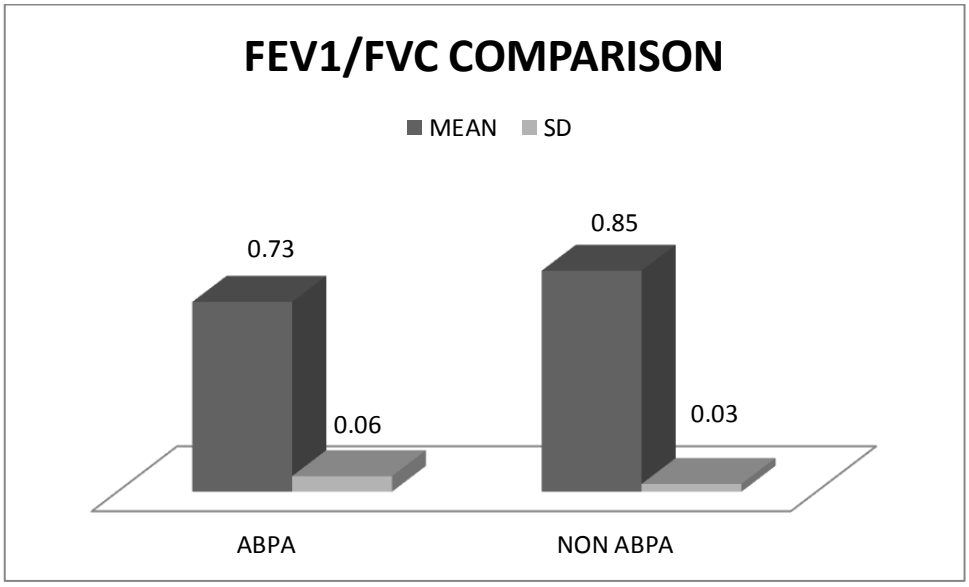
P value <0.0004 statistically significant value.



CORRELATION BETWEEN POST TREATMENT COMPARISON OF FEV1/FVC

	ABPA (n=19)	Non ABPA(n=81)
Mean	0.73	0.85
SD	0.06	0.03

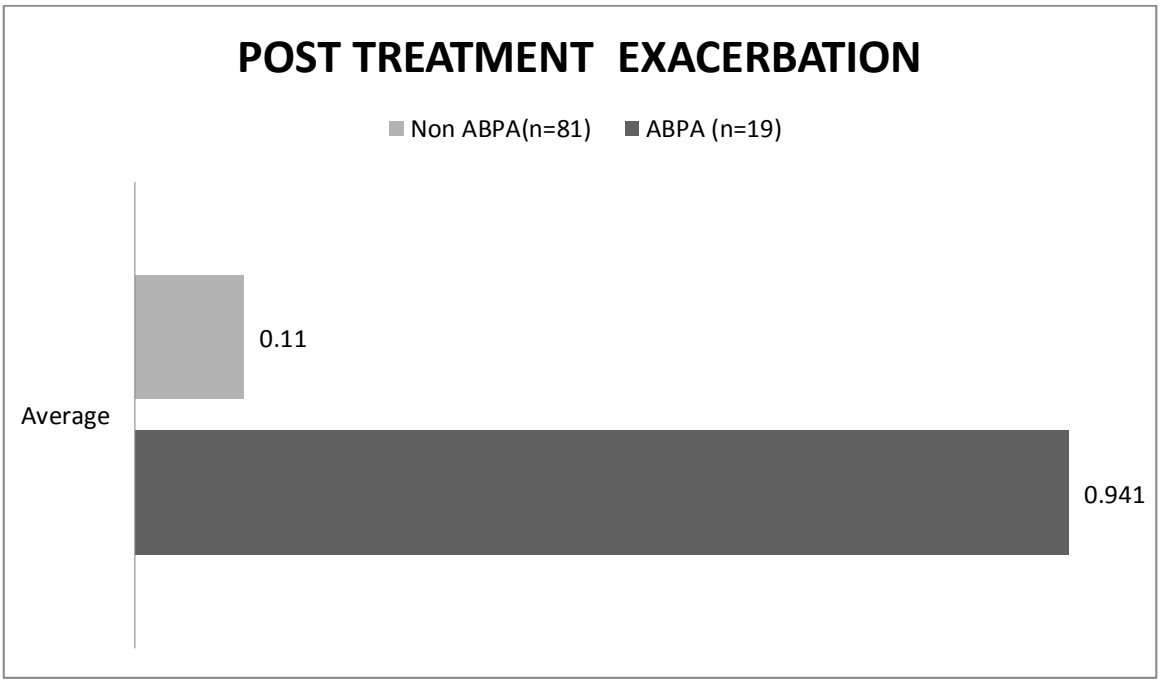
P value is <0.0001 statistically significant



CORRELATION BETWEEN POST TREATMENT EXACERBATIONS

Post treatment exacerbation	ABPA (n=19)	Non ABPA(n=81)
Average	0.941	0.11
SD	0.70	0.31

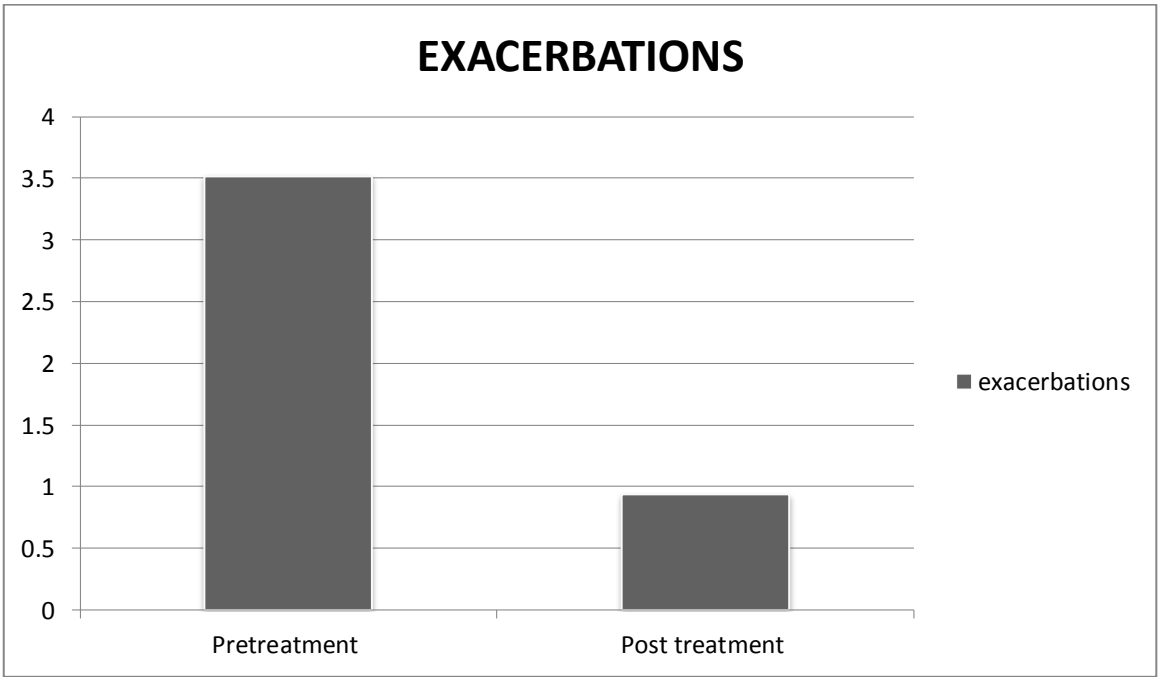
P value is<0.001 statistically significant



Comparison between pre treatment and post treatment exacerbations in ABPA patients

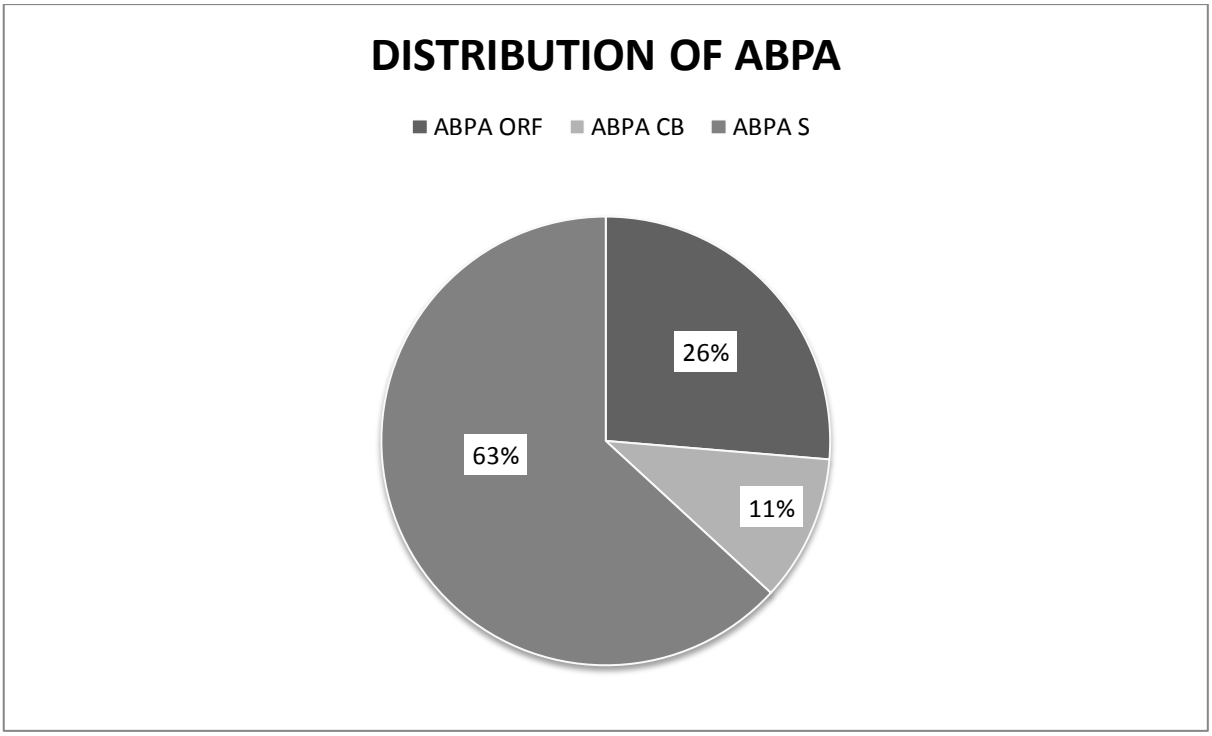
	Exacerbations (mean value)
Pretreatment	3.52±1.17
Post treatment	**0.94±0.7**

P value<0.001, statistically significant



Stages of ABPA:

Stages of ABPA	No. Of patients
ABPA ORF	5
ABPA-CB	2
ABPA-S	12



ORF other radiological feature

CB central bronchiectasis

S serological

Characteristics of ABPA S patients:

Patient characteristics/variables	Results/values(n=12)
Total number	12 persons
Average age (in years)	35.33±11.06
No. Of male patients	5 out of 12
No. Of female patients	7 out of 12
Average duration (in years)	13.95±8.6
Family history positive	10out of 12
Skin prick test positive	12 out of 12
Average absolute eosinophil count (cells/cu mm)	1365.5±481.3 2311.91±502.26
Average ige value (iu/dl)	7 out of 12
Sputum koh positive	3 out of 12
History of atopy	3.3±0.88
Mean value of exacerbation prior to treatment	96%±3%
Average spo2	2 out of 12
History of smoking	0.833±0.71
Average exacerbation after treatment	0.76±0.005
Average post treatment FEV1/FVC ratio	

COMPARISON OF CHARACTERISTICS AMONG DIFFERENT TYPES OF ABPA

Characteristics	ABPA-S	ABPA-ORF	ABPA-CB	P value
Age(in years)	35.33±11.06	29.8±11.07	40.5±10.6	>0.05
Duration(in years)	13.95±8.6	16.2±13.42	21±18.38	>0.05
Absolute eosinophil count(cells/cu mm)	1365.5±481.3	1105±450.416	1610±93.3	>0.05
Serum IgE level(IU/dl)	2311±502.26	2053.4±539.19	232.5±14.84	<0.0002
Pre treatment exacerbation	3.3±0.88	3.8±1.2	4 ±0	>0.04

COMPARISON OF CHARCTERISTICS AMONG THE TYPES OF ABPA:

Events	**TYPES OF ABPA**			**P value**
	Serology	**ORF**	**CB**	
Post treatment exacerbation	0.833±0.71	1.2±0.83	1±0	0.63
Spo2	96±3	96±2	92±1	0.17
FEV1/FVC	0.761±0.05	0.70±0.05	0.67±0	0.02

Variable	Mean difference	Comparison	P value	Significance
Post treatment exacerbation	258.51	SEROLOGY VS ORF	>0.005	No
Spo2	2079.4	SEROLOGY VS CB	<0.001	Yes
FEV1/FVC	1820.9	ORF VS CB	<0.01	Yes

DISCUSSION

AGE AND GENDER:

In our study of 100 patients of refractory and resistant Asthma with difficulty to treat history, 19% of them were positive for ABPA. Previous Indian statistics suggest that the prevalence of ABPA is 3-4% in Asthmatics, of which 15% belong to the category of Steroid Sensitive patients. Around 3-14% of other related diseases also had ABPA.

Around 19% of patients, which is a significant number belonging to various stages of ABPA, with definitive radiological evidence like bronchiectesis and related findings were present in our study. In our study the total number of ABPA-S was 12 and proximal bronchiectasis were 5 and mucus plugs, fibrosis were 2 in number. Our patients were analysed with respect to age distribution and the mean age group is 36.67 years, which correlates with previous studies like AGARWAL et al.

Our study shows. female were 11 in number and males were 8 in number.

By comparing male to female ratio, the relative risk is 0.091 which is not significantly showing gender difference, as the literature tells that there is no gross sex predilection, except in the extremes of ages.

DURATION OF ASTHMA PERIOD

While linking duration of the disease in years, our study showed that between 5-10years there were 9 patients and between 10-20 years, there were 4 patients. When the duration of the illness was more than 20 years, 6 patients had ABPA., As per our study, duration of this disease does not correlate with the prevalence thereby inferring chronicity and severity were not parallel. Correlating with the previous study, severity is linked with the sensitivity to pathogens and not the chronicity of the asthma prevalence.

FAMILY HISTORY

Among 100 patients, 48 persons had family history of asthma. Among 100 selected asthmatics, 17 out of 19 persons with ABPA had positive family history. Thus assuming the fact that familial propensity is present in ABPA, and presence of hereditary causes (as discussed earlier) is a standing proof for their correlation. Since so many HLAs and other

factors were linked in previous study, a strong familial predisposition is present.

ATOPY HISTORY:

Atopy in the study group is significantly associated with the predilection of ABPA. 14 out of 19 patients are atopic individuals which is coherent with the previous study correlating with the subtypes. 2 out 2 persons with central bronchiectasis are atopic individuals where as atopic history is absent in 3 out of 12 asthmatics . In the non ABPA asthmatics only 12 out of 81 patients are atopic which has a negative predictive value.

SMOKING HISTORY:

Only 3 persons out of 19 ABPA patients were smokers, thus suggesting that risk of smoking is not significant in the pathobiology of ABPA as in COPD, but immune dysregulation has still has a role in cause.

SKIN INTRADERMAL TEST:

The study group was analyzed with intradermal test, which is more are less a screening test. The test showed 17 out of 19 ABPA were positive

for skin prick test. On the other group (non ABPA group), skin prick test was negative in all the individuals. With this significance, our study has showed remarkable association of skin prick test in predicting the prevalence of ABPA.

ABSOLUTE EOSINOPHIL COUNT:

In our study the average value is 1322.73 cells/cu mm. On the other group (non ABPA) average value is 288.135

Eosinophil count has more relevance in establishing the ABPA diagnosis. The number of eosinophils counts has pivotal role in the diagnosing ABPA case among the asthmatics. Comparing with the previous study conducted by Greenberg Paterson et al, which shows similar results, the role of eosinophils in diagnosing ABPA is re emphasized.

SERUM IMMUNOGLOBULIN E level:

Among the ABPA diagnosed, 2245.48 IU/dl is the average value of IgE levels. Comparing with the non ABPA groups patients, who were found to have lesser levels of statistical significance. Group of patients with high IgE levels were found to have no predilection to gender. But it

has correlation to severity of disease and severity of radiological manifestations.

RADIOLOGY:

Chest X- Ray and the CT chest have definite value in diagnosing ABPA. ABPA with proximal bronchiectasis was present in 2 out of 19 patients. Proximal bronchiectasis has more specific value, than the other types of bronchiectesis. No abnormal imaging pattern was present in the non ABPA group (81 patients). Abnormal finding was present in 7 out of 19 patients in the ABPA group.

OXYGEN SATURATION SPO_2 :

Most of the ABPA patients in our study group were maintaining good saturation except for those with severe structural lung disease. But it has limitations in its comparative value, among the ABPAs.

TYPES OF ABPA:

Of the 3 types of ABPA identified in our study, ABPA S was the most commonly identified type.

EXACERBATION REDUCTION:

Exacerbation is one of the serious clinical manifestation in patients with ABPA. As per our study, pretreatment exacerbation average was 3.52. Compared with non ABPA group, it was statistically significant. In patients with ABPA, exacerbations before and after treatment were compared. The number of exacerbations reduced drastically in this group of 19 patients. Hence, treatment with prednisolone and itraconazole in reducing the exacerbations is identified. ALIF et al correlates ABPA with the frequency in exacerbation.

CONCLUSION:

1. The prevalence of allergic Bronchopulmonary aspergillosis in the treatment resistant Bronchial Asthma patients was 19% percentage in this study and it is comparatively little higher than the previous studies conducted.
2. Positive family history, history of atopy and history of recurrent exacerbations were identified as risk factors among the study group.
3. Complications like bronchiectasis and parenchymal damage, was seen in significant number among the study groups.
4. Duration of Asthma and severity has no direct link between each other.
5. Skin prick test is a good screening test to identify ABPA patients among asthmatics.
6. Sputum test for potassium Hydoxide mount has shown good number of positive results but cannot be used as a screening test.
7. Blood values of eosinophils and IgE antibody levels highly correlate with ABPA positivity among asthma patients.

8. Significant differences in lung function were observed between ABPA and non ABPA groups.
9. Exacerbations are reduced after treatment in good number of patients, efficacy of prednisolone and Itraconazole, are highly reliable and test outcome has good.

In refractory cases of asthma, ABPA must be considered as possible diagnosis.

BIBLIOGRAPHY

1. Radin RC, Greenberger PA, Patterson R, Ghory A. Mould counts and exacerbations of allergic bronchopulmonaryaspergillosis. Clin Allergy 1983;13:271

2. Patterson R, Greenberger PA, Radin RC, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med1982;96:286–2911.

3. Hinson KF, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis; areview and a report of eight new cases.Thorax 1952;7:317–3333

.4. Reiff DB, Wells AU, Carr DH et al. CThfindings in bronchiectasis: limited value in distinguishing between idiopathic andspecific types. AJR Am J Roentgenol1995;165:261–267.

5. Lee TM, Greenberger PA, Patterson R,Roberts M, Liotta JL. Stage V (fibrotic)allergic bronchopulmonary aspergillosis. A review of 17 cases followed from diagnosis. Arch Intern Med1987;147:319–323.

6. Greenberger PA, Patterson RJ. Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. *J AllergyClin Immunol* 1988;81:646-

7. Neeld DA, Goodman LR, Gurney JW,Greenberger PA, Fink JN. Computerized tomography in the evaluation ofallergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1990;142:1200–120

.8. Angus RM, Davies ML, Cowan MD, Mcsharry C, Thomson NC. Computed
tomographic scanning of the lung in patients with allergic bronchopulmonary aspergillosis and in asthmatic patients with a positive skin test to Aspergillus fumigatus. Thorax 1994;49:586–589.

9. Ward S, Heyneman L, Lee MJ, Leung AN, Hansell DM, Muller NL. Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. AJR Am J Roentgenol1999;173:937–942.
10. Shah A, Khan ZU, Chaturvedi S, et al. Concomitant allergic aspergillus sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis. *Ann Allergy* 1990;64:507-51.
11. Chauhan B, Santiago L, Kirschmann DA, et al. The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. *J Immunol* 1997;159:4072-6.
12. Chauhan B, Santiago L, Hutcheson PS, et al. Evidence for theinvolvement of two different MHC class II regions in susceptibility or protection in allergic bronchopulmonary aspergillosis. *J AllergyClin Immunol* 2000;106:723-9.
13. Chauhan B, Knutsen AP, Hutcheson PS, et al. T cell subsets, epitope mapping, and HLA-restriction in patients with allergicbronchopulmonary aspergillosis. *J Clin Invest* 1996;97:2324-31.
14. Wark PA, Hensley MJ, Saltos N et al.Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. J Allergy Clin Immunol 2003;111:952–957.
15. Wark PA, Gibson PG, Wilson AJ.Azoles for allergic bronchopulmonary aspergillosis associated with asthmaCochrane Database Syst Rev2003;3:CD001108.
16. Mccarthy DS, Pepys J. Allergic bronchopulmonaryaspergillosis. Clinical immunologyI. Clinical features. Clin Allergy1971;1:261–286

17Stevens DA, Schwartz HJ, Lee JY et al.A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000;342:756–762.

18Salez F, Brichet A, Desurmont S, Grosbois JM, Wallaert B, Tonnel AB. Effects of itraconazole therapy in allergic bronchopulmonaryaspergillosis. Chest 1999;116:1665–1668.

19. Middleton WG, Paterson IC, Grant IW,Douglas AC. Asthmatic pulmonary eosinophilia: a review of 65 cases. Br J Dis Chest 1977;71:115–122. . Neeld DA, Goodman LR, Gurney JW,Greenberger PA, Fink JN. Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis.
Am Rev Respir Dis 1990;142:1200–1205

20. Capewell S, Chapman BJ, Alexander F,Greening AP, Crompton GK. Corticosteroid treatment and prognosis in pulmonary eosinophilia. Thorax1989;44:925–929.

21 Neeld DA, Goodman LR, Gurney JW,Greenberger PA, Fink JN. Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1990;142:1200–1205

22 Rosenberg M, Patterson R, Mintzer R,Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977;86:405–414

22. Mccarthy DS, Pepys J. Allergic bronchopulmonary aspergillosis. Clinical immunology. Skin, nasal and bronchial tests. Clin Allergy 1971;1:415–432.

23. Dessaint JP, Bout D, Fruit J, Capron A.Serum concentration of specific IgE antibody against Aspergillus fumigates and identification of the fungal allergen. Clin Immunol Immunopathol1976;5:314–319.

24. Ricketti AJ, Greenberger PA, PattersonR. Serum IgE as an important aid inmanagement of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 1984;74:68–71.
25. Greenberger PA, Liotta JL, Roberts M.The effects of age on isotypic antibody responses to Aspergillus fumigatus:implications regarding in vitro measurements.J Lab Clin Med 1989;114:278–
26. Apter AJ, Greenberger PA, Liotta JL, Roberts M. Fluctuations of serum IgA and its subclasses in allergic bronchopulmonary aspergillosis. J Allergy ClinImmunol 1989;84:367–372.
27. Gibson PG, Wark PAB, Simpson JL, et al. Induced sputum IL-8 gene expression, neutrophil influx and MMP-9 in allergic bronchopulmonary aspergillosis. *Eur Respir J* 2003;21:582-8.
28. Denning DW, O'Driscoll BR, Hogaboam CM, et al. The link betweenfungi and severe asthma: a summary of the evidence. *Eur Respir J*2006;27:615-26.
29. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J AllergyClin Immunol* 2002;110:685-92.
30. Slavin RG, Bedrossian CW, Hutcheson PS et al. A pathologic study of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 1988;81:718–725.
31. Jelihovsky T. The structure of bronchial plugs in mucoid impaction, bronchocentric granulomatosis and asthma. *Histopathology* 1983;7:153–167.
32. Fraser R, Mu¨ ller N, Colman N, Pare´ P. Fungi and actinomyces In: Fraser RS, Pare´ PD, editors. Diagnosis of diseases of the chest.Philadelphia: Saunders Company, 1999:875–978.

33. Hanson G, Flor N, Wells I, Novey H, Galant S. Bronchocentric granulomatosis: a complication of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 1977;59:83–90.
34. Koss MN, Robinson RG, Hochholzer L. Bronchocentricgranulomatosis. *Hum Pathol* 1981;12:632–638.
35. Berendsen HH, Hofstee N, Kapsenberg PD, van Reesema DR, KleinJJ. Bronchocentric granulomatosis associated with seropositivepolyarthritis. *Thorax* 1985;40:396–397.
36. Katzenstein AL, Liebow AA, Friedman PJ. Bronchocentric granulomatosis, mucoid impaction, and hypersensitivity reactions to fungi. *Am Rev Respir Dis* 1975;111:497–537.
37. Hellems SO, Kanner RE, Renzetti AD Jr. Bronchocentricgranulomatosis associated with rheumatoid arthritis. *Chest*1983;83:831–832.
38. Fraser R, Mu¨ ller N, Colman N, Pare´ P. Fungi and actinomyces. In: Fraser RS, Pare´ PD, editors. Diagnosis of diseases of the chest.Philadelphia: Saunders Company, 1999:875–978.
39. Gibson PG. Allergic bronchopulmonary aspergillosis. *Semin RespirCrit Care Med* 2006;27(2):185-90.
40. Slavin RG, Hutcheson PS, Chauhan B, et al. An overview of allergic bronchopulmonary aspergillosis with some new insights. *AllergyAsthma Proc* 2004;25:395-9.
41. Kumar R. Mild, moderate, and severe forms of allergic bronchopulmonary aspergillosis. A clinical and serologicevaluation. *Chest* 2003;124:890-2.
42. Greenberger PA, Patterson R. Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. *J Allergy Clin Immunol* 1988;81:646– 650.

43. Schwartz HJ, Greenberger PA. The prevalence of allergic bronchopulmonary aspergillosis in patients with asthma,determined by serologic and radiologic criteria in patients at risk.*J Lab Clin Med* 1991;117:138–142.
44. Knutsen A, Slavin RG. Allergic bronchopulmonary mycosis complicating cystic fibrosis. *Semin Respir Infect* 1992;7:179–192.
45. Stevens DA, Moss RB, Kurup VP et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis – state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003;37(Suppl.3):S225–S264.
46. Zeaske R, Bruns WT, Fink JN et al. Immune responses to Aspergillus in cystic fibrosis. *J Allergy Clin Immunol* 1988;82:73–77.
47. Silverman M, Hobbs FD, Gordon IR, Carswell F. Cystic fibrosis, atopy, and airways liability. *Arch Dis Child* 1978;53:873–877.
48. Nikolaizik WH, Moser M, Crameri R et al. Identification of allergic bronchopulmonary aspergillosis in cystic fibrosis patients by recombinant Aspergillus fumigatus I/a-specific serology. *Am J Respir Crit Care Med* 1995;152:634–639.
49. Stevens DA, Moss RB, Kurup VP et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis-state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003;37(Suppl.3):S225–264.
50. Patterson R, Greenberger PA, Radin RC, et al. Allergic bronchopulmonary aspergillosis: staging as an aid to management.*Ann Int Med* 1982;96:286-91.
51. Lee TM, Greenberger PA, Patterson R, et al. Stage V (fibrotic) allergic bronchopulmonary aspergillosis: a review of 17 cases followed from diagnosis. *Arch Intern Med* 1987;147:319-23.

52. Tillie-Leblond I, Scherpereel A, Iliescu C. Aspergillose bronchopulmonaire allergique. *Rev Fr Allergol Immunol Clin* 2002;42:231–240.
53. Reiff DB, Wells AU, Carr DH et al. CT findings in bronchiectasis:limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol* 1995;165:261–267.
54. Mintzer RA, Rogers LF, Kruglik GD, Rosenberg M, Neiman HL, Patterson R. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology* 1978;127:301–307.
55. Murphy D, Lane DJ. Pleural effusion in allergic bronchopulmonary aspergillosis: two case reports. *Br J Dis Chest* 1981;75:91–95.
56. Neeld DA, Goodman LR, Gurney JW, Greenberger PA, Fink JN. Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1990;142:1200–1205.
57. Angus RM, Davies ML, Cowan MD, Mcsharry C, Thomson NC. Computed tomographic scanning of the lung in patients with allergic bronchopulmonary aspergillosis and in asthmatic patients with a positive skin test to Aspergillus fumigatus. *Thorax* 1994;49:586–589.
58. Nichols D, Dopico GA, Braun S, Imbeau S, Peters ME, Rankin J. Acute and chronic pulmonary function changes in allergic bronchopulmonary aspergillosis. *Am J Med* 1979;67:631–637.
59. Greenberger PA, Patterson R, Ghory A et al. Late sequelae of bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 1980;66:327–335.
60. Patterson R, Greenberger PA, Lee TM et al. Prolonged evaluation of patients with corticosteroid-dependent asthma stage of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 1987;80:663–668.

61. Basich JE, Graves TS, Baz MN et al. Allergic bronchopulmonary aspergillosis in corticosteroid-dependent asthmatics. *J Allergy Clin Immunol* 1981;68:98–102.
62. Lee TM, Greenberger PA, Patterson R, Roberts M, Liotta JL. Stage V (fibrotic) allergic bronchopulmonary aspergillosis. A review of 17 cases followed from diagnosis. *Arch Intern Med* 1987;147:319–323.
63. Safirstein BH, D'souza MF, Simon G, Tai EH, Pepys J. Five-year follow-up of allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1973;108:450–459.
64. Fournier EC. Trial of ketoconazole in allergic bronchopulmonary aspergillosis. *Thorax* 1987;42:831.
65. Stevens DA, Schwartz HJ, Lee JY et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000;342:756–762.
66. Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. Cochrane Database Syst Rev 2003;3:CD001108. Allergic bronchopulmonary aspergillosis.

ABBREVIATIONS

ABPA	ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS
BA	BRONCHIAL ASTHMA
SPT	SKIN PRICK TEST
AEC	ABSOLUE EOSINOPHIL COUNT
AE	ACUTE EXACERBATIONS
FEV1	FORCED EXPIRATORY MINUTE VOLUME
FVC	FUNCTIONAL VITAL CAPACITY
ABPA-S	SEROLOGICAL TEST POSITIVE
ABPA-CB	CENTRAL BRONCHIECTASIS
ABPA-ORF	OTHER RADIOLOGICAL FEATURES
GMS	GOMARRI METHANAMINE SILVER
PAS	PERIODIC ACID STAIN
PEFR	PEAK EXPIRATORY FLOW RATE
CF	CYSTIC FIBROSIS

PROFORMA

Name: Age: Sex:
Education:
Address:
Unit/Ward:
ID number:
INFORMANT : Self / Other RELATION

PRESENT HISTORY

Day of onset of the symptoms
Time of onset of the symptoms
Treatment obtained prior to admission

PAST and PERSONAL HISTORY

Bronchial Asthma	ONSET/DURATION	
Diabetes Mellitus	Yes / No	Duration
Hypertension	Yes / No	Duration
Pulmonary TB	Yes / No	Duration
Atopy	Yes / No	Duration
COPD	Yes / No	Duration
Bronchiectesis	Yes / No	Duration
Dyslipidemia	Yes / No	Duration
Alcoholism	Yes / No	Duration
Smoking	Yes / No	Duration
Medications		

FAMILY HISTORY

Hypertension Yes/No
Duration
Diabetes Yes/No
Duration
Coronary artery disease Yes/No
Duration
COPD Yes / No Duration
Bronchial Asthma Yes / No Duration

PREGNANCY/PUERPERIUM AT PRESENT Yes /No

VITALS

Pulse rate : /min

Blood Pressure :

/ mm Hg Limb: RUL / LUL Posture: /sitting / Supine

Respiratory Rate : /mt

ANTHROPOMETRY

Height : m

Weight : kg

BMI : kg / m^2

Waist Hip Ratio

CVS :

Respiratory system :

Abdomen examination :

CNS examination :

INVESTIGATIONS:

COMPLETE HEMOGRAM

Hemoglobin : g/dL

Total Count : cells/cu.mm

Differential count :

RBC Count : cells/cu.mm

Platelets : lakhs/cu. mm

BLOOD BIOCHEMISTRY

Random Blood Sugar : mg/dL

Blood Urea : mg/dL

Serum Creatinine : mg/dL

Serum sodium : meq/l

Absolute Eosinophil count : dl/bld.

Skin Prick Test : + / -

LIVER FUNCTION TESTS

1. Total bilirubin : mg/dl.
2. AST : IU/L.

3. ALT : IU/L.
4. Total proteins : grams/dL.
5. Albumin : grams/d

CHEST XRAY

PULMONARY FUNCTION TEST

SERUM IGE LEVEL

PEAK EXPIRATORY FLOW RATE

CT CHEST

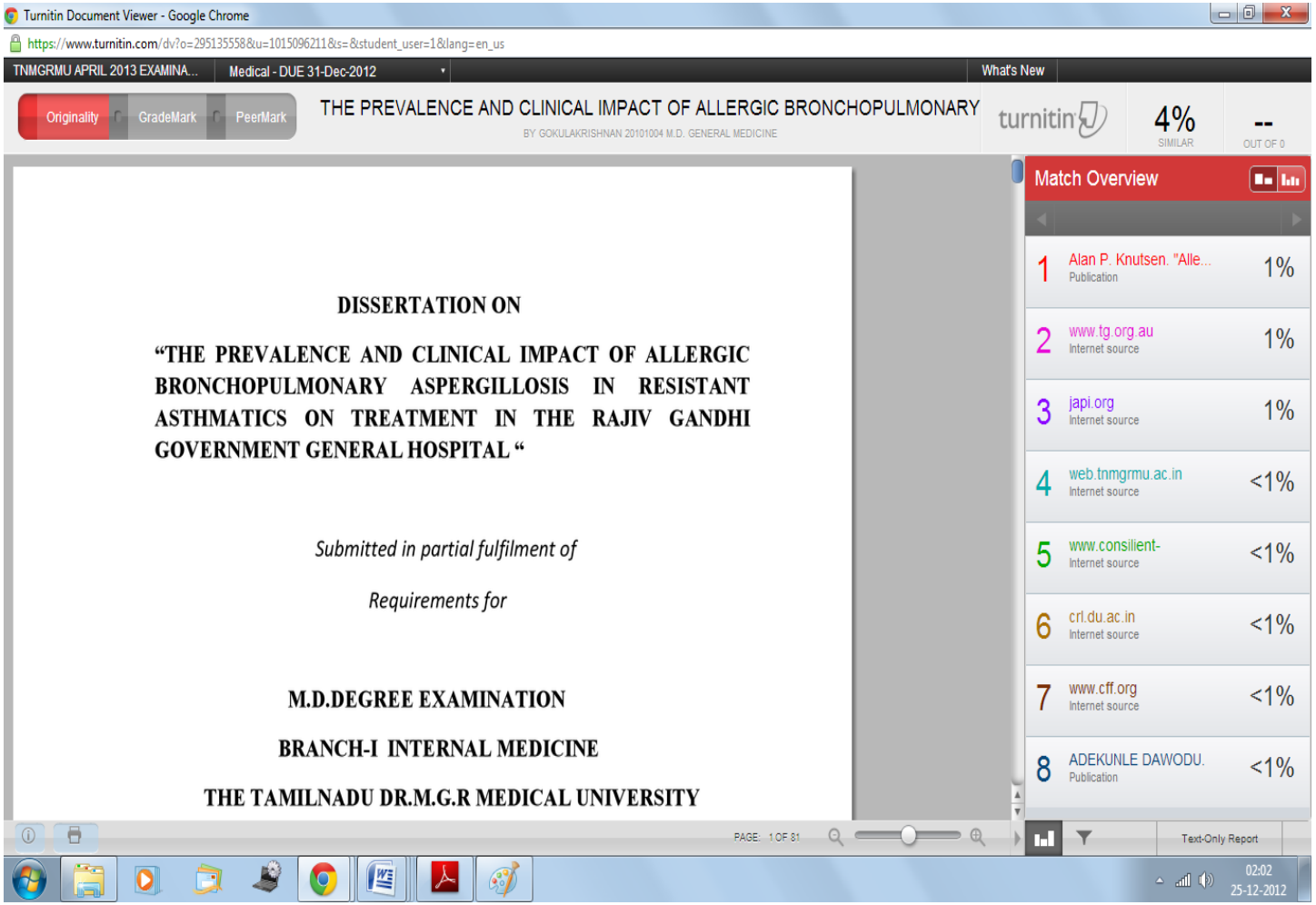
s.no	name	age	sex	duration of asthma	family history	skin prick test	absolute eosinophilcount	serum IGE level	xray chest	CTchest	sputum koh mount for fungalfilaments	stage of ABPA	h/o atopy	NO OF EXACERBATION 3MONTHS PRIOR TO STUDY	pulse oximetry	smoking	EXACERBATIONS AFTER TREATMENT	post treatment FEV1/FVC ratio
1	Raja	43	M	23	Y	Y	1879	2543	N	N	Y	ABPA-s	y	3	0.99	yes	1	0.68
2	Alima	40	F	40	N	N	87	246	N	N	N	N	y	1	0.98	no	0	0.81
3	chellammal	36	F	10	Y	Y	1500	1675	N	N	N	N	n	1	0.99	no	0	0.82
4	saravanan	30	M	5	N	N	97	453	N	N	N	N	n	1	0.99	yes	0	0.88
5	sandhya	18	F	5	Y	Y	1660	2300	N	N	Y	ABPA-s	n	3	0.96	no	1	0.68
6	kanaga	33	F	8	N	N	900	1100	N	N	N	N	n	1	0.98	no	0	0.72
7	jothi	30	F	25	Y	N	350	560	N	N	N	N	y	1	0.98	no	0	0.86
8	susila	30	F	6.5	Y	Y	800	1900	N	N	Y	ABPA-S	y	4	0.96	no	0	0.78
9	sarasu	45	F	22	N	N	64	54	N	N	N	N	n	1	0.99	no	0	0.88
10	meenakshi	50	F	28	N	N	344	566	N	N	N	N	n	1	0.98	no	0	0.86
11	vijaya	48	F	34	Y	Y	1544	2333	B	B	Y	ABPA-CB	y	4	0.92	no	1	0.67
12	chinnathabi	32	M	6	N	P	1023	2500	N	N	P	ABPA-S	y	2	0.91	yes	0	0.75

13	jayammal	29	F	23	N	N	234	409	N	N	N	N	n	1	0.94	no	0	0.81
15	vijaya	16	F	9	N	N	60	445	N	N	N	N	n	2	0.99	no	0	0.86
16	kanniyammal	50	F	23	Y	Y	2166	3465	N	N	N	ABPA-S	n	4	0.91	no	2	0.86
17	sarasu	35	F	3	N	N	45	456	N	N	N	N	n	1	0.98	no	0	0.86
18	sanjammal	45	F	38	Y	N	890	1656	FB	FB	N	ABPA -ORF	n	5	0.97	no	2	0.72
19	kasthuri	42	F	34	N	N	54	345	N	N	N	N	n	1	0.99	no	0	0.88
19	nagappan	34	M	8	Y	Y	1600	2300	FB	FB	N	ABPA-ORF	y	6	0.97	yes	2	0.79
20	kamala	60	F	20	N	N	56	233	N	N	N	N	n	0	0.99	no	0	0.88
21	pandammal	40	M	29	N	N	23	321	N	N	N	N	n	1	0.98	no	0	0.88
22	sathyavathi	25	F	20	Y	Y	440	1432	FB	FB	Y	ABPA-ORF	n	1	0.92	no	0	0.71
23	logammal	49	F	10	N	N	60	154	N	N	N	N	y	1	0.99	no	0	0.85
24	dhanam	44	F	39	N	P	550	1453	N	N	N	N	n	1	0.97	no	1	0.82
25	gopalan	33	M	8	Y	Y	1676	2312	B	B	Y	ABPA-CB	y	4	0.91	no	1	0.67
26	krishnan	42	M	29	Y	N	45	243	N	N	N	N	n	1	0.98	yes	1	0.88
27	kumar	45	M	15	N	N	56	342	N	N	N	N	n	1	0.96	yes	0	0.86
28	beevi	40	F	18	N	N	67	182	N	N	N	N	n	1	0.97	no	0	0.88
29	kamala	60	F	14	N	N	109	388	N	N	N	N	y	1	0.99	no	0	0.87
30	pandamml	40	F	5	Y	Y	1561	2387	N	N	N	ABPA-S	n	5	0.99	no	1	0.72
31	padma	30	F	5	Y	Y	1256	2800	FB	FB	N	ABPA-ORF	y	3	0.96	no	1	0.67
32	venkat	22	M	10	Y	Y	908	1300	N	N	N	N	y	1	0.92	yes	0	0.81
33	raja	45	M	35	Y	Y	1243	2456	N	N	N	N	y	3	0.96	yes	0	0.83
34	azarudeen	18	M	4	Y	N	67	330	N	N	N	N	n	1	0.99	no	0	0.84
35	sendurkani	40	M	5	N	N	78	800	N	N	N	N	n	1	0.98	yes	0	0.88

36	muniammal	35	F	5	Y	N	134	454	N	N	N	N	n	1	0.98	no	0	0.87
37	durairaj	55	M	6	N	N	45	220	N	N	N	N	n	1	0.99	no	1	0.85
38	vijay kumar	15	M	10	Y	N	1340	2079	MC	MC	Y	ABPA-ORF	y	4	0.96	no	1	0.65
39	mythili	41	F	14	Y	Y	60	1338	N	N	N	N	y	1	0.97	no	0	0.81
40	rajammal	47	F	22	Y	Y	1100	2079	N	N	N	N	y	3	0.97	no	0	0.83
41	nagappan	39	M	6	N	N	65	133	N	N	N	N	n	1	0.98	no	0	0.91
42	hemavathy	34	F	12	N	N	167	657	N	N	N	N	n	1	0.98	no	0	0.89
43	raja	16	M	10	N	N	1167	2345	N	N	P	N	n	1	0.99	no	0	0.81
44	vinoth	29	M	12	Y	Y	1450	2453	N	N	Y	ABPA-S	y	4	0.93	no	1	0.81
45	revathi	28	F	7	Y	N	67	342	N	N	N	N	n	1	0.98	no	1	0.89
46	rani	34	F	18	N	N	453	1776	N	N	N	N	n	2	0.99	no	0	0.86
47	anbalagan	56	M	30	N	N	344	1221	N	N	N	N	n	5	0.99	no	0	0.84
48	fathima	43	F	17	N	N	122	309	N	N	N	N	n	2	0.98	no	0	0.89
49	parimala	28	F	12	Y	Y	1600	2335	N	N	N	ABPA-s	y	3	0.97	no	0	0.78
50	kavitha	28	F	15	N	N	213	322	N	N	N	N	n	1	0.99	no	1	0.82
51	keerthana	24	F	2	N	N	342	768	N	N	N	N	n	1	0.97	no	0	0.87
52	yasodha	54	F	35	N	N	45	769	N	N	N	N	n	1	0.99	no	0	0.86
53	ramani	42	F	13	Y	Y	456	1324	N	N	N	ABPA-s	y	4	0.98	no	1	0.81
54	pratheep	27	M	17	N	N	56	432	N	N	N	N	n	1	0.98	no	0	0.89
55	karthick	27	M	5	N	N	74	452	N	N	N	N	n	1	0.99	no	0	0.87
56	sudhakar	32	M	23	N	N	132	700	N	N	N	N	n	1	0.99	yes	0	0.84
57	suresh	34	M	7	N	N	220	346	N	N	N	N	n	1	0.99	yes	0	0.86
58	valli	43	F	23	N	N	120	122	N	N	N	N	n	0	0.98	no	0	0.84

59	sumathi	36	F	20	N	N	210	654	N	N	N	N	n	0	0.98	no	0	0.89
60	sivagami	32	F	21	N	N	225	153	N	N	N	N	n	0	0.99	no	0	0.88
61	vijayaragav	45	M	23	Y	N	45	344	N	N	N	N	n	0	0.98	yes	0	0.91
62	sathyavathi	24	F	20	Y	Y	1564	2314	N	N	N	N	y	2	0.99	no	1	0.79
63	parthioban	39	M	12	N	N	231	453	N	N	N	N	n	1	0.97	no	0	0.88
64	sundar	36	M	28	N	N	69	153	N	N	N	N	n	0	0.98	no	0	0.86
65	venkatram	47	M	23	Y	Y	1567	2343	N	N	N	ABPA-s	y	3	0.97	no	2	0.76
66	prabakar	36	M	13	N	N	342	674	N	N	N	N	n	1	0.99	yes	0	0.84
67	usha	31	F	18	N	N	456	1643	N	N	N	N	n	2	0.98	no	0	0.81
68	natraj	45	M	30	N	N	560	1430	N	N	N	N	n	2	0.98	no	0	0.91
69	ranjith	18	M	9	Y	Y	1004	1882	N	N	N	ABPA -s	y	2	0.99	no	0	0.82
70	hari	38	M	4	Y	N	322	342	N	N	N	N	n	1	0.99	no	0	0.84
71	naveen	16	M	9	N	N	67	1323	N	N	N	N	n	2	0.98	no	0	0.83
72	alamelu	37	F	5	N	N	89	323	N	N	N	N	n	1	0.97	no	0	0.82
73	perumal	42	M	22	N	N	54	784	N	N	N	N	n	0	0.98	no	0	0.79
74	vasanta	36	F	24	N	N	57	565	N	N	N	N	n	0	0.99	no	0	0.82
75	chandra	57	F	30	N	N	343	435	N	N	N	N	n	0	0.98	no	0	0.91
76	arjunan	35	M	19	N	N	563	1121	N	N	N	N	n	3	0.97	yes	0	0.81
77	arundathi	22	F	17	Y	N	476	1354	N	N	N	N	y	4	0.98	no	1	0.79
78	kokila	38	F	10	Y	N	56	332	N	N	N	N	y	1	0.97	no	0	0.88
79	rani	38	F	4	Y	N	480	1334	N	N	N	N	n	2	0.98	no	1	0.86
80	preethi	17	F	4	Y	N	440	1034	N	N	N	N	y	2	0.96	no	0	0.88
81	iyappan	32	M	23	N	N	561	1181	N	N	N	N	n	1	0.98	yes	0	0.81

82	nagaraj	40	M	17	N	N	459	1068	N	N	N	N	n	1	0.98	yes	0	0.85
83	puspa	25	F	12	Y	N	43	453	N	N	N	N	n	0	0.97	no	0	0.82
84	moorthy	31	M	20	N	N	67	234	N	N	N	N	n	0	0.99	yes	0	0.84
85	chellapa	45	M	25	N	N	56	122	N	N	N	N	n	0	0.99	yes	0	0.84
86	bakiam	45	F	8	N	N	70	124	N	N	N	N	n	0	0.99	no	0	0.91
87	dhanalaksmi	25	F	19	N	N	89	234	N	N	N	N	n	0	0.98	no	0	0.81
88	mary	47	F	35	Y	N	65	206	N	N	N	N	n	0	0.98	no	0	0.86
89	ragini	40	F	29	Y	N	60	105	N	N	N	N	n	0	0.98	no	0	0.87
90	laksmi	36	F	8	N	N	78	243	N	N	N	N	n	1	0.94	no	0	0.81
91	poongothai	47	F	30	N	Y	1220	2311	N	N	P	ABPA-s	y	3	0.95	no	1	0.69
92	kamaksi	36	F	15	N	N	112	344	N	N	N	N	n	2	0.98	no	0	0.81
93	jeya	38	F	23	N	N	667	980	N	N	N	N	n	1	0.98	no	0	0.84
94	durai	41	M	9	N	N	230	650	N	N	N	N	n	1	0.97	yes	0	0.84
95	annamalai	38	M	25	Y	N	69	230	N	N	N	N	n	0	0.99	no	0	0.83
96	senthilkumar	26	M	18	N	N	430	789	N	N	N	N	n	0	0.98	no	0	0.81
97	mariyal	39	F	29	Y	N	675	1221	N	N	N	N	n	3	0.98	no	1	0.72
98	pryadarsini	24	F	15	N	N	450	900	N	N	N	N	n	1	0.99	no	0	0.88
99	lillibai	35	F	5	N	N	239	560	N	N	N	N	n	1	0.98	no	0	0.86
100	amirtha	40	F	28	Y	N	347	543	N	N	N	N	n	1	0.98	no	0	0.82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Submitted in partial fulfilment of
Requirements for
M.D.DEGREE EXAMINATION
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